Vol. 24 No. 120 December, 1949

ARCHIVES OF DISEASE IN CHILDHOOD

INCORPORATING THE BRITISH JOURNAL OF CHILDREN'S DISEASES

CONTENTS

(Index to Volume 24 included)

LONDON
BRITISH MEDICAL ASSOCIATION
TAVISTOCK SQUARE, W.C.1

YEARLY SUBSCRIPTION (4 NUMBERS) 25s. U.S.A. $6.00 SINGLE NUMBER 7s. 6d.

NOTICE TO SUBSCRIBERS

Subscriptions are payable to the British Medical Association. Address : British Medical Association House, Tavistock Square, London, W.C.1.

NOTICE TO CONTRIBUTORS

Papers submitted to this journal are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal, and are subject to editorial revision. All papers and other editorial communications should be addressed to Dr. Philip R. Evans, Department of Child Health, Guy's Hospital, London, S.E.1. The author of an original article should make adequate references to previous work on his chosen subject. A full summary of his observations and conclusions must be given.

Articles must be as concise as possible and be typewritten on one side of the paper only, with double spacing and a margin of not less than 1½ in. Only recognized abbreviations should be used. Graphs, charts, tables, and legends for them should be presented on separate sheets and not included in the text. When half-tone reproduction of x-ray illustrations is required, the author is advised to send the original film unless he wishes to bring out special points in a print of his own choice. Photographs and photomicrographs should be printed on glossy paper, should be larger than the size desired for reproduction, and, if transmitted through the post in a tube, should be rolled with the picture outside. With the exception of letters and numbers, which should be lightly written in pencil, everything that is to appear in the reproduction of a graph or chart should be carefully drawn in black ink on tracing linen, or Bristol board, or stout, smooth, white paper.

References should be arranged according to the Harvard system. In the text, the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. No numbering of references is necessary. At the end of the contribution references are arranged in the alphabetical order of the authors' names. The reference details are given as follows : Author's name and initials, year of publication (in parentheses), title of periodical (in italics, abbreviated according to the *World List of Scientific Periodicals*), volume number (bold type, Arabic numerals), and first page number (ordinary type, Arabic numerals) thus :

Cowan, J. (1929). *Quart. J. Med.*, **22**, 237.

When a book is referred to, the place and year of publication, edition, and page number should be given.

Contributors will receive one proof, but it is assumed that all but verbal corrections have been made in the original manuscript ; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Fifty free reprints of articles will, if desired, be given to contributors. A limited number of additional reprints at cost price can be supplied if application is made when returning proofs. An estimate of costs will be given on application to the Publishing Manager, British Medical Association.

Papers which have been published become the property of this Journal, and permission to republish must be obtained from the Editor.

Application for advertisement space should be addressed to the Advertisement Manager, British Medical Association, Tavistock Square, London, W.C.1 (Euston 2111).

Subscription 25s. per annum, post free (20s. to members of the B.M.A.).

THE TREATMENT OF DIABETES IN CHILDHOOD*

BY

A. LICHTENSTEIN

(From the Paediatric Clinic of the Caroline Institute, the Crown Princess Louisa's Hospital, Stockholm)

The treatment of diabetes in children has interested me now for thirty-five years. In the pre-insulin days I saw the sufferings of diabetic children, who were confined to a diet extremely reduced in carbohydrates and containing practically none of the kind of food that children like. And, in spite of these sufferings, they were condemned to an early death.

Then came insulin which made a rich carbohydrate diet possible. One might have expected a rapid change in diabetic management. This, however, was not the case. On the contrary, during the first insulin years one generally attempted to control the disease as long as possible by reducing the carbohydrate intake and withholding insulin until it was impossible to continue treatment with diet alone. Since that time more liberal ideas on the diabetic diet have slowly spread. Gradually the diet has been brought into closer correspondence with that of healthy persons. So far, however, most diabetes specialists have hesitated to take the decisive step of changing over to a quite normal diet. Moreover, ideas on the diets of diabetics are still highly inconsistent. Different types of diet are prescribed with a highly varying content of calories, as well as of protein, fat, and carbohydrate. This was cleverly demonstrated by Barach in a paper read at the annual meeting of the American Diabetes Association in 1944. He compared the allowances per day for diabetic children at different ages by various groups; for instance, by the Medical Research Council in England, by the National Research Council in the United States, and by the League of Nations Committee. Barach concluded that, depending upon which of these standards one happened to accept, we would prescribe from 20 to 300 per cent. more or less of calories, and the same lack of agreement holds true for the allowance of the different constituents of the food. We find, for instance, for protein 100 per cent. variation in the daily allowance. And for whichever standard we might adopt we would have a recognized authority in every instance. It is astonishing that these and similar facts have not led to the conclusion that no ground exists for the acceptance of a scientifically founded restricted diet, prescribed in every detail.

Our Present Knowledge of Nutritional Requirements of Diabetes

It may be useful to review shortly our present knowledge of the diabetic's need of food and of its various constituents. There are no valid reasons for assuming a greater caloric need for the diabetic than for a non-diabetic individual of the same age. Nor has any conclusive evidence been advanced for the supposition that the diabetic child needs more protein than the non-diabetic one. The question of the fat allowance is closely connected with the carbohydrate intake. In the past fat made up a large part of the caloric intake of the diabetic. To-day, however, the need of a well-balanced diet for the formation and decomposition of ketone bodies is generally accepted, and consequently the fat allowance has been reduced to about 20 to 30 per cent. of the total caloric intake, that is, the same as in the normal diet.

About half of the caloric intake of normal adults and children consists of carbohydrates. Because of the nature of diabetic metabolism, the carbohydrates obviously had to be greatly reduced in the pre-insulin era. With the introduction of insulin a more liberal carbohydrate allowance became possible. To-day, 40 to 50 per cent. of the caloric intake of many diabetics is composed of carbohydrates, although many physicians still cling to a more restricted carbohydrate intake.

In estimating the carbohydrate allowance for a diabetic it is necessary to remember first that the diabetic organism is deficient in glycogen and has to struggle against a dysfunction in the formation and deposition of glycogen in the liver, and secondly that the carbohydrates are, in Macleod's phrase, the fuel of life even for the diabetic. A sufficient carbohydrate intake, made possible through insulin, is and must be the cornerstone in the treatment of a diabetic. Long ago we also learned from Allen and Dubois that a diabetic utilizes the carbohydrates in spite of hyperglycaemia and glycosuria, and this has been confirmed in many quarters.

* A paper read at a meeting of the British Paediatric Association, 1949.

The knowledge that sugar is formed both from protein and fat has thrown a new light on the question of the intake of the various food constituents. Geelmuyden states that all three, protein, fat, and carbohydrate, mingle inseparably in the intermediary metabolism, react mutually, and form new combinations, and that it is impossible to determine which of them is the primary source of the new-built sugar. Soskin and Levine also point out that ' in the light of more recent knowledge of intermediary metabolism, it seems likely that we shall soon cease to distinguish between the metabolisms of the different foodstuffs, once they have gone beyond certain stages, for eventually all of them give rise to very similar intermediary products, namely the α- and β-keto acids,' and they speak of ' a final common pathway for all the foodstuffs.'

Our present knowledge of the importance of vitamins for the diabetic can be summarized as follows.

There is no evidence of a lack of vitamin A in diabetics. At least three elements of the vitamin B complex are of importance for the carbohydrate metabolism. Thiamine pyrophosphate is the co-enzyme necessary for the oxidation of pyruvic acid. The yellow enzyme, necessary in hexose oxidation, is now known to be a riboflavin phosphate and protein combination. One of the co-enzymes involved is nicotinic acid. Despite the important role of the vitamin B complex in carbohydrate metabolism it seems evident that the diabetic generally receives so much from the food that surplus amounts are of no importance in the treatment of diabetes. My observations agree with Joslin's that no notable effect on the blood sugar or insulin requirement can be observed, even when large doses are given.

Patients with uncomplicated diabetes and adequate vitamin C intake have normal plasma levels of ascorbic acid. Hamne found that the injection of 200 to 500 mg. of ascorbic acid, intravenously, somewhat intensified the action of insulin on the blood sugar level. Owens et al., however, gave diabetics 300, 600, and 1,200 mg. of ascorbic acid daily without noting any constant improvement. My own experience points in the same direction. It would seem, therefore, that diabetics, provided their intake is adequate, have no greater need of vitamin C than normal individuals. Nothing of special importance is known of the diabetic's requirements of vitamins D, E, and K.

While the importance of the mineral salts in diabetes is unquestioned, a mixed diet of natural foods which is adequate in other respects will also provide a sufficient amount of the minerals.

To sum up: it should be emphasized that in recent years there has been increasing agreement that the diabetic needs an adequate, normal, well balanced diet with an ample supply of vitamins, that is, a diet based on modern knowledge of the physiology of nutrition.

Experiments with ' Free Diets '

It was such considerations as these which led some paediatricians some twenty years ago to raise the question: Does a proper control of diabetes in children require a strictly regulated diet or is it possible to control the disease with insulin only, without dietetic restrictions ?

It is not a mere coincidence that the treatment of diabetes without dietetic restrictions has been taken up by paediatricians. Diabetes in children is essentially different from diabetes in adults, and the difficulties incidental to a more or less rigorous diet make themselves much more strongly felt in children than in adults.

In children, diabetes is almost always severe. It is, moreover, characterized by a more labile metabolism than in adults, with sudden oscillations between hyperglycaemia and hypoglycaemia and with a perpetual menace of ketosis. Children are also more liable to infection. Furthermore, diabetic children require an adequate supply of food for growth and development, whereas adult diabetics need only be maintained in equilibrium and can even periodically be kept with advantage on a somewhat low diet.

Last but not least we must take into account the psychological factors. The maintenance of a diet which is to be observed not for weeks or months but for life is harmful to mental development, character formation, and social adjustment. There is no doubt that the diabetic regimen produces behaviour difficulties in children. But we want the diabetic child to develop in a normal way not only physically but also mentally. We should therefore, as far as possible, avoid placing these children in a position apart from other children, and I see in this an important reason in favour of the ' free diet.'

The first experiences in the treatment of diabetes in children without any dietetic restrictions were published in 1931 by Stolte in Breslau. In 1933 Söderling in Stockholm reported a number of good results obtained through the same method. In 1932 I tried the effect of the ' free diet ' on a minor scale. In fact one patient of mine has had the ' free diet ' since 1924. He is still living in good general health and without any signs of arteriosclerosis. Since 1933 I have consistently carried out treatment with the ' free diet.' I mean by this term a normal diet corresponding completely with that of healthy children. The diabetic children are allowed to share the diet of their brothers and sisters, to eat their fill and to satisfy their individual tastes within the same limits as healthy children. Even sugar and sweets, in reasonable amounts, are permitted. The only restriction is avoidance of over-indulgence, just as one would impose on any child. The ' free diet ' is thus a normal, balanced, all-round fare, which is not the case with high-fat, high-protein, and high-carbohydrate diets.

The amounts of food which the diabetic children spontaneously consume in the hospital are weighed and measured. As a rule, the children take 150 to

TABLE 1
DAILY FOOD INTAKE OF DIABETIC CHILDREN

Age (years)	Barach, 1944				Collens and Boas, 1946				'Free Diet'			
	Calories	*Carbo-hydrate	Protein	Fat	Calories	Carbo-hydrate	Protein	Fat	Calories	Carbo-hydrate	Protein	Fat
1–3	85–110	10–14	3–4	3·5–4	90–100	11–12	3–4	3–4	90–100	10–11	3	3–3·5
4–6	78–80	10	3	3·2–3·5	80–90	10–11	3–3·5	3–3·5	80–90	7–10		
7–9	64–72	8–9	2·5–3	2·6–3	70–80	9–10	2·5–3	2·5–3	70–80			
10–12	56–63	7–8	2·0–2·3	2–2·5	60–70	7–9	2·5–3	2·5–3	50–70	6–7	2–3	2·5–3
13–15	44–55	6–7	1·8–2·0	2	50–60	7–9	2–2·5	2·5–3	40–60			

* All values in rounded g. per kg. body-weight.

250 g. carbohydrate per day, corresponding to 6 to 7 g. per kilogram of body-weight per day, with relatively small variations from day to day. Younger children consume considerably more, up to 8 to 10 g. or more per kilogram of body-weight per day. Some older children, periodically, also seem to show a relatively large need of carbohydrates. Of protein, the children consume, as a rule, 2 to 3 g., and of fat 2·5 to 3·5 g. per kilogram of body-weight per day.

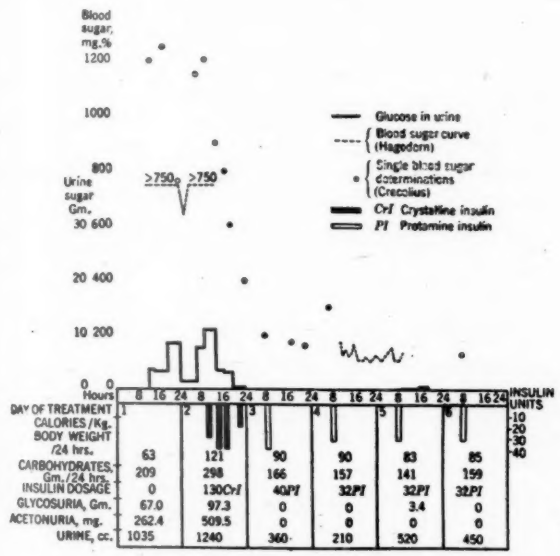

FIG. 1.—Chart showing control in a fresh case.

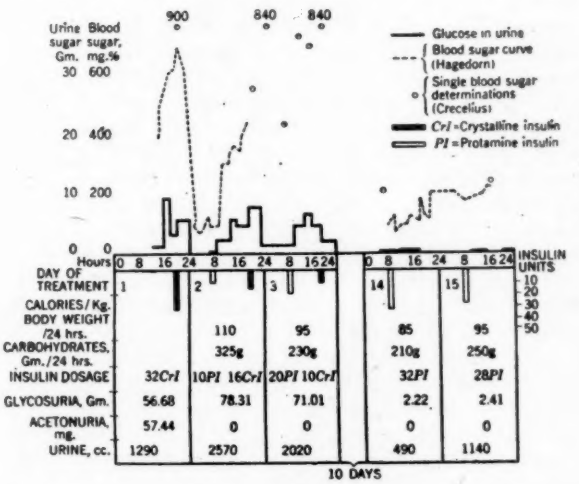

FIG. 2.—A second chart showing control in a fresh case.

The supply of calories was as a rule spontaneously maintained at 80 to 100 under 5 years of age, at 60 to 80 between 5 and 10 years, and at 40 to 60 between 10 and 15 years, all per kilogram of body-weight.

It is of interest to compare the average supply of food on the 'free diet' with the allowances of calories, carbohydrate, protein, and fat in recent diets prescribed for diabetic children. Table 1 shows the allowance in Barach's diet (1944) and in that of Collens and Boas (1946), compared with the spontaneous intake of Swedish children on a 'free diet.'

From the table it may be gathered that the amounts of carbohydrates, protein, and fat which are prescribed in diets for diabetic children in part considerably exceed the spontaneous intake of my patients. In fact, there exist prescribed diets with more carbohydrate and less carbohydrate, with more protein and less protein, with more fat and less fat, than the normal diet of healthy Swedish children.

Naturally, my own experience applies only to Swedish children. The figures cited cannot simply be transferred to all countries, in view of the great variations in different parts of the world. Everyone must be aware of the difference in the diet of the Eskimos and the Negroes. However, it is probable that the Swedish figures are applicable in countries where the normal diet is a balanced one, satisfactory from the modern point of view of the physiology of nutrition.

A fresh case of diabetes is always given the ordinary hospital fare. In most cases control is

obtained within a few days or at most a week, as is shown on figs. 1 and 2. I consider a patient under control when he has a feeling of well-being, has a normal appetite, normal thirst, a normal quantity of urine, and is free of all subjective symptoms. It has, however, not been my aim to keep the urine sugar-free, provided the child is otherwise symptom-free. I think some tens of grams of sugar per twenty-four hours are permissible. As a rule, the degree of glycosuria is less than 10 per cent. of the carbohydrate intake. It is obvious that there is a slighter risk of hypoglycaemia under such circumstances than with attempts to obtain a completely sugar-free urine. Moreover, I think Lawrence is right when he states that no case of severe diabetes can be kept continuously sugar-free without risk of hypoglycaemia by any present method of insulin treatment which is tolerable to the patient. And I agree with him also when he says that such an ambition may stimulate the diabetic purist but is a curse to his patient. In my patients severe hypoglycaemic attacks are rare. They occur occasionally when there is intercurrent acute disease with loss of appetite or vomiting, or when children are taken out of their normal routine and have meals irregularly, as for example, during a long journey.

Permitting a slight glycosuria I do not aim at 'normalizing' the blood sugar level. One cannot take for granted that what is a normal blood sugar level in a non-diabetic individual is necessarily 'normal' for a diabetic. Actually many authors have stressed the importance of a glucose level in the blood sufficient for the storage of glycogen in the liver. In reality, one should adhere to the aim that the diabetic utilizes carbohydrates as completely as possible in comparison with his need; in other words, that the carbohydrate balance, the difference between intake and excretion, should be as great as possible. It must always be remembered that it is utilization and not excretion that is important.

Of course, it is not at all difficult to depress the blood sugar level; it is only necessary to reduce the quantity of food, but that in no way implies that the utilization of carbohydrates has improved. On the contrary, we know that starvation, as well as a diet high in fat in comparison with the carbohydrates, will lead to fatty infiltration of the liver. The blood sugar may then be 'normalized'; however, 'the diabetes is better, but the patient is worse.'

In my opinion, when the increase in the blood sugar level is limited, no attempt need be made to bring the level down to normal. This should not be taken to mean that the blood sugar may be allowed to rise to many hundred milligrams per 100 ml. In well controlled cases on the 'free diet' the fasting values of the blood sugar usually range between 100 and 200 mg. per 100 ml. The twenty-four-hour curve often shows considerable variations, but that is also true of diabetic children on a restricted diet.

Non-normalization of the blood sugar has caused no difficulty in any of our cases. Assuming that the rise in blood sugar is moderate, there is no difficulty in keeping the patient symptom-free in other respects. An unfavourable effect of a somewhat higher blood sugar was not demonstrable on either the frequency and course of infections or the frequency of complications.

Although a small or moderate excretion of sugar is permitted in our patients, ketonuria is not. In our opinion, scrupulous attention to this plays a decisive role in the favourable course of diabetes treated by 'free diet.' As Bertram, among others, points out, it is the ketosis and not the blood sugar level which is responsible for a severe course of the disease. It was found that the 'free diet' greatly aided our efforts to keep patients free of ketosis, and that a previously marked tendency towards ketosis frequently disappeared when patients were transferred to it. Children with constant signs of ketonuria, who in many cases were repeatedly sent to hospital because of menacing or full-blown coma, after removal of all dietetic restrictions for years showed no trace of ketonuria. Compared with our previous experience, the frequency of pre-coma and coma was markedly reduced by the 'free diet.'

Now, in the light of my experience, I think it is established that diabetic children on the 'free diet' grow and develop in a normal way, pass through puberty normally, are able to work physically and mentally, and show a considerably stronger resistance to acute infections, as well as to tuberculosis, than do patients treated with a diet restricted in carbohydrates. The former also show a considerably lower frequency both of coma and of hypoglycaemic attacks. In each of these respects, treatment with insulin and without any dietetic restrictions is undoubtedly at least as valuable, and, from certain points of view, probably superior to treatment with diet plus insulin.

The 'Free Diet' and the Frequency of Complications

Evaluation of any method of treating diabetes requires, however, not only consideration of these circumstances but also of the frequency of various complications. Many authors have in the last years reported an alarming frequency of cardiovascular and ocular complications in juvenile diabetic patients who have been treated for ten to twenty or more years. Particularly remarkable are White's figures of known vascular complications in 203 (or 92 per cent.) of 220 cases (table 2). These

TABLE 2

VASCULAR DISEASE IN 220 CASES OF JUVENILE DIABETES SURVIVING TWENTY YEARS OR MORE OF THE DISEASE (WHITE)

	Per cent.
Retinal arteriosclerosis	85
Retinal haemorrhages	75
Calcified arteries	70
Hypertension	55
Albuminuria	40
Coronary insufficiency	7
Cerebral vascular accidents	2

are indeed frightening, especially when one considers that the source is perhaps the best organized institution for the treatment and control of diabetes with a restricted and carefully controlled diet. White, it is true, says that ' these are the worst possible statistics which will ever be presented since these patients did not receive modern treatment for 50 per cent. of their diabetic lives.' But insulin treatment has been used for twenty-five years now. Dolger's figures are even worse; in 200 regularly examined patients he found ' no single instance where the diabetes had lasted twenty-five years in which the patient escaped the development of vascular damage.' It seems not improper to point out that a method of treatment giving such a high degree of severe complications is in great need of improvement.

A priori, it is not very probable that treatment with the ' free diet ' will prove to be considerably superior to treatment by diet, in so far as frequency of complications is concerned. In fact, the differences between prescribed diets and the ' free diet ' often are insignificant, even though a low-carbohydrate diet is still often prescribed. We need new discoveries. Perhaps the newer knowledge of the pituitary and adrenal hormones may lead to as yet untouched means of therapy. One can only hope that work such as that of the Coris, of Houssay, and of their followers will finally give the clinicians better weapons for preventing complications.

However, the actual question here is whether the frequency of complications on the ' free diet ' is higher, lower, or equal to the complications which arise on the restricted diets. From this point of view, proof that the frequency of complications is not higher on the ' free diet ' should suffice. The possibility that the ' free diet ' will give a reduced frequency of complications is not excluded, but it is too early for a definite statement in this matter.

What do we know about the causative factors of the cardiovascular complications ? It would entail too long a discussion to take up the whole problem, so I must limit myself to a few points. First, it may be stated that the arteriosclerotic lesions complicating juvenile diabetes on the whole are identical with those seen in persons of advanced years. The assumption is therefore justified that the etiology, at least in part, is the same. Even reckoning with the many different causes contributing to the development of arteriosclerosis, constitutional and hereditary factors, senescence, as well as disturbances in the hormonal balance and toxic and mechanical causes, a great many facts speak in favour of the concept that nutritional causes in the form of a disturbed lipid metabolism and acid-base balance are concerned in the development of cardiovascular lesions in diabetes. We know that it is possible to produce arteriosclerosis of the human type in animals by feeding them cholesterol. We also know that increase in blood cholesterol is a regular phenomenon in arteriosclerosis in man. Now, poorly controlled or uncontrolled diabetes is often associated with a considerable increase of blood cholesterol and the cholesterol level rises with the severity of the disease. It thus seems obvious that there is a close relation between cardiovascular disease in diabetes and hypercholesteraemia.

Ketosis seems also to be important in the development of arteriosclerosis. We know that a ketogenic diet provokes a high blood pressure in rabbits and that the changes are more severe in animals in which the acid-base balance is much disturbed. The blood fat varies in diabetes with the acidosis. It may therefore be supposed that a ketogenic diet plays a role in the development of arteriosclerosis in juvenile diabetes. As already pointed out the frequency of coma was reduced by the ' free diet.' On the other hand the assumption that there is some connexion between high blood sugar levels and the appearance of cardiovascular lesions has not been confirmed.

From these points of view, it seems reasonable that the carbohydrate-rich ' free diet ' may be of some value in preventing or postponing juvenile arteriosclerosis. In any case, nothing favours the opinion that a diet poor in carbohydrates, that is, to a certain extent a ketogenic diet, is preferable in this respect.

In my report in 1945 on ten years' experience with the ' free diet ' I had to describe few complications. Since then I have had the same experience as Priscilla White, Dolger and others that vascular complications become more and more frequent after the tenth year of diabetes.

Our own cases are now being systematically re-examined for complications. The data are still incomplete. To-day I am only able to give preliminary figures on about fifty cases with a history of diabetes of over twelve years. We have found albuminuria in about 30 per cent., hypertension also in about 30 per cent., calcified arteries in about 14 per cent., and retinal haemorrhages or other pathological findings in the eyes in about 60 per cent. However, in most cases with retinal haemorrhages there were no subjective symptoms. Only in about 13 per cent. could a considerable visual reduction be demonstrated.

So far it seems that vascular eye complications in my patients occur with about the same frequency as in patients treated with a restricted diet, but that hypertension, and particularly calcification in the peripheral arteries, occur somewhat less frequently.

The high frequency of vascular damage is, however, appalling, and I agree with Priscilla White that vascular disease in diabetes must be considered a challenging problem for future solution. To-day we can only state that the duration of the diabetes is, in Dolger's phrase, ' the only unequivocal factor in the determination of the appearance of vascular damage.'

To sum up, I should like to point out that our present knowledge does not justify the assumption that the danger of vascular damage is greater in diabetics on the ' free diet ' than in those on restricted diets. If anything, the contrary is probable.

For the present, however, this is only a hypothesis. A mere ten to fifteen years of observation are an inadequate basis for judging the frequency of diabetic complications, and with the exception of a few cases, treatment with the ' free diet ' is not yet twenty years old. In five to ten years it will be possible to be more positive in answering this question. The real problem to-day in judging the value of any method of treating diabetes is its capability of preventing complications.

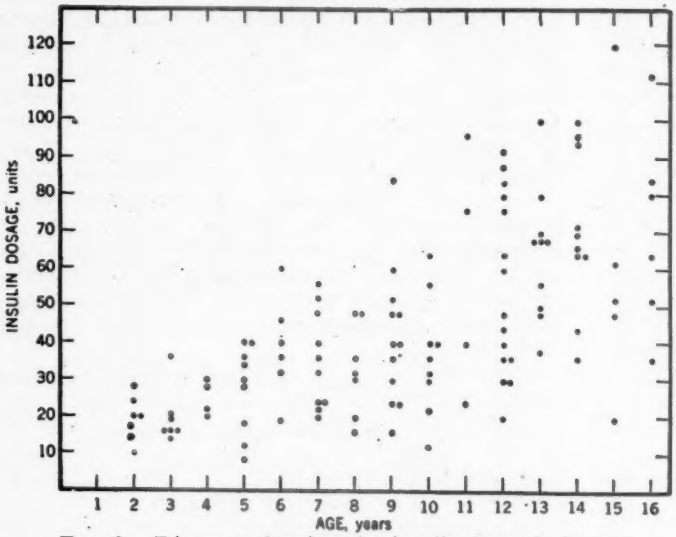

FIG. 3.—Diagram showing the insulin dose during the second year of the ' free diet '.

The mortality rate is, of course, also of great importance. For a number of reasons, however, comparisons between the various rates is particularly difficult in diabetes. Thus, it is possible to draw comparisons only with great reserve, and the best statistics for this purpose are those from one and the same country.

A comparison between published figures with strictly prescribed diets and with the ' free diet ' covering a period of fifteen years' treatment shows that the mortality rate of diabetes on the ' free diet ' does not suffer by comparison with the results on the restricted diet. Difficult as it is to arrive at exact comparisons, it yet seems obvious that the mortality rate of our patients on the 'free diet' for fifteen years, about 6 per cent., is not higher and is probably lower than the best results achieved with restricted diets.

The overall picture of fifteen years' treatment of diabetes in children without dietetic restrictions is thus a very satisfactory one: good physical and mental development, a minimum of coma and hypoglycaemia, a frequency of complications not higher and possibly lower than in treatment with restricted diets, and a low mortality.

Conditions of Success Using the ' Free Diet '

The essential conditions for satisfactory results with the ' free diet ' are, first, adequate insulin treatment from the outset, and second, careful continuous control.

Insulin supply. An adequate insulin supply is the prerequisite for every satisfactory diet for diabetic children. The first consideration is the choice of the preparation. Previously, treatment without dietetic restrictions required two, and often three, doses of ordinary insulin a day. Now that we have obtained new insulin preparations with a slow absorption time, treatment has been simplified. I have used Hagedorn's protamine insulin with great advantage, and have been able in most cases to reduce the number of injections to one a day. As a rule, it is given in the morning, about half an hour before the first meal. In a small number of cases, an evening dose is also required. Sometimes it is of advantage to combine protamine with a dose of crystalline insulin at the same time. No account has been taken of the endogenous liver rhythm, nor was there any necessity for this in my material. In most cases, zinc protamine insulin was found to be less beneficial for children. On this insulin, they showed a tendency to hypoglycaemia more frequently than on the protamine insulin without zinc. Occasionally, however, one finds a child who adjusts himself more easily to the insulin with zinc than without it. In a single case, the old type of insulin was found to be superior to the protamine type. It is evident that in the choice of preparation proper allowance must be made for individual differences.

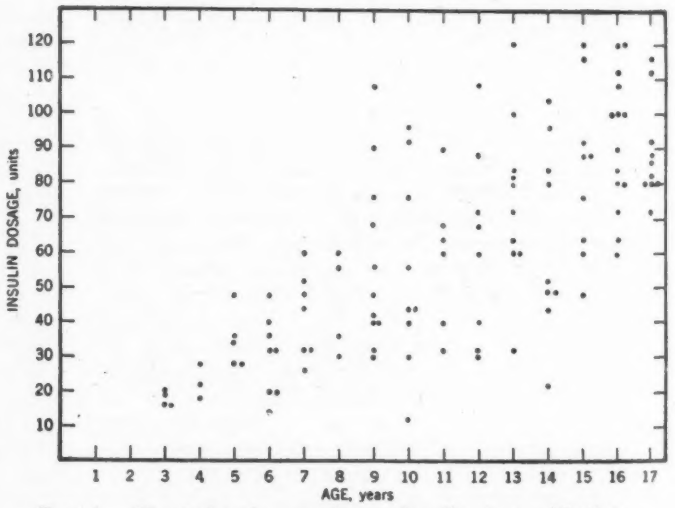

FIG. 4.—Chart showing maximum insulin dose with the ' free diet '.

The insulin requirement varies greatly from case

to case, and must be individually tested for each child. Especially in the initial stage of the disease, very careful control and flexibly adjusted changes in the insulin supply are required.

To gauge the insulin requirement of a diabetic child being treated without dietetic restrictions, the insulin dosage should be observed for a sufficiently long time after treatment is instituted, if necessary, during the second year even, by which time practically all cases attain a certain stability in insulin requirement. Fig. 3 shows the relation between the patient's age and the insulin requirement, and the variation in the amount of insulin required; the dosages range from 10 to 120 international units per day, with an average of about 40 units.

Fig. 4 shows the maximum insulin requirements of our patients at any time during the observation period, attacks of coma excluded. Here, too, the range is between 10 and 120 units, but the average, about 60 units, is of course higher.

Control of the case. Careful, continuous control is essential if good results are to be obtained with a normal diet. Examinations must be frequent at first; gradually, they can be spaced further apart. When the patients are children, such control involves good co-operation with the home, especially with the mother. Mothers must, therefore, be taught the principal features of the clinical treatment of the disease. It is particularly important that mothers learn the significance of increased thirst and large amounts of urine as signs of unsatisfactory adjustment, and the importance, in such cases, of consulting the doctor immediately. Mothers must also learn to recognize the signs of hypoglycaemia and how to counteract it. Stress should be laid on the importance of a regular conduct of life and regular meals.

Summary

The 'free diet' has been adopted by many physicians, particularly in the Scandinavian countries and in Germany, and numerous reports have been published on the results in juvenile diabetes as well as in adults. On the basis of the published material, it would seem that those using this treatment are satisfied with the results. Nevertheless, the method has met with violent opposition. This was to be anticipated, since it called for a break with the long-fixed concept of the necessity of a restricted diet in the treatment of diabetes.

Various arguments have been used by those objecting to the 'free diet.' I have already dealt with most of these. A further objection has been that the 'free diet' would considerably increase the insulin requirement. As early as 1929 Richardson demonstrated that carbohydrates might be substituted for fat in the diet without increasing the insulin dosage. The amount of insulin required by patients on the 'free diet' has been about the same as by diabetics on a restricted diet. This has been confirmed by a recent study of a large group of diabetic patients in Sweden: the average amount of insulin per day and per individual required by 915 patients of varying ages, who carefully followed a strict prescribed diet, was 52 units, whereas 4,639 patients on the 'free diet' needed an average of 56 units daily. That is an insignificant difference. Patients with a ten-year duration of the disease used an average of 65 units daily, whether they had kept to a restricted diet (256 cases) or were on a normal diet (1,333 cases).

In spite of all opposition, the 'free diet' gains ground every day. One important reason for this is the difficulty, not to say impossibility, of keeping a patient on a strictly regulated diet for decades. According to Joslin, 'breaking the diet and cheating the doctor are infrequent episodes to-day.' But his co-worker, White, states:

'Incorrectly kept (perfect) urine charts, the substitution of water for a specimen of urine, the substitution of an obliging normal friend's urine for the patient's own, while annoying to the physician, should not be considered abnormal behaviour for the juvenile diabetic.'

In the Swedish investigation we found that of 5,207 diabetics of all ages only 35·7 per cent. carefully followed the instructions regarding diet. Thus two-thirds of all patients followed their prescribed diets carelessly or not at all. I doubt if similar investigation in other countries would give a better result. Is it not wiser to give the diabetic freedom to eat the food which is normal for his home, age, and work, and adjust the insulin dosage for control under these circumstances rather than to prescribe a diet which in the long run only one-third of the patients follow and thereby run the risk of insufficient control and perhaps insufficient insulin dosage? True, the insulin requirement of patients on the 'free diet' is on the average not much higher than that of patients on restricted diets. Nevertheless, in the individual case, there may be a difference of 10 per cent. or more, a difference which can be of great importance for the control of the disease.

Many physicians who still prescribe a diet now declare that this diet should be a normal one. The difference between the advocates of the 'free diet' and those who prescribe a normal diet is obviously only the answer to the question: Is it necessary to prescribe a normal diet in the form of a detailed diet chart or is it not sufficient to prescribe a regular conduct of life and avoidance of overfeeding? I for my part am convinced that a normal diet can be maintained without any other restrictions than the ones just mentioned.

In my opinion the many objections to the 'free diet' have not stood the test of time. Finally I wish once more to stress that psychological considerations favour the 'free diet.' Liberation of a diabetic child from its position of being different from other children must be beneficial to the child's mental development, character formation, and social adjustment. It is well known that mental strain has an unfavourable effect on diabetes. I believe that a feeling of well-being, on the contrary, has a favourable effect. Is it not time for those who impose restrictions on their patients to show that their results are better than control with insulin alone and without restrictions ?

STUDIES IN COELIAC DISEASE: FAT ABSORPTION

BY

WILFRID SHELDON, M.D., F.R.C.P., and ANTOINETTE MACMAHON,* M.B., Ch.B.
(From the Hospital for Sick Children, Great Ormond Street, London)

Reasons were given in 1948 (Sheldon) for thinking that in coeliac children starch intolerance might be of greater etiological significance than a failure to absorb the products of fat digestion. In a later communication (Sheldon, 1949), from a study of fat balances in a group of fifteen children with coeliac disease, it was concluded that withdrawal of starch from the diet was accompanied by a rise in fat absorption averaging 15 per cent.

Dietary Dextrin and Fat Absorption

The mechanism by which dietary starch in coeliac children interferes with the absorption of fat is not at present understood, but the question arises whether this effect is attributable to undigested starch, or whether the first product of starch digestion, namely dextrin, also interferes with fat absorption. To test this, it was decided to carry out fat balances on a small number of coeliac children, performing a balance first of all on a starch-free diet, and then repeating it after changing to a diet which should be not only starch-free, but the starch should be replaced as far as was practicable by dextrin.

The amount of dextrin in a normal diet is quite small, probably of the order of from 1 to 5 per cent. of the total carbohydrate, but the proportion of dextrin in the special starch-free diets that had been used in the previous balance experiments was definitely greater. A recent analysis of these diets shows that the dextrin content averaged 20 per cent. of the total carbohydrate, the remainder consisting of cane sugar, fructose, and glucose.

Previous experience with fat balance investigations had indicated that the period of a balance could be reduced from twelve to eight days without losing

TABLE 1

RESULTS OF FAT BALANCE INVESTIGATIONS ON FOUR CHILDREN WITH COELIAC DISEASE

	Starch-free Diet		Starch-free Diet (with extra dextrin)	
Case	Diet	Percentage Fat Absorption (8-day period)	Diet	Percentage Fat Absorption (8-day period)
M.B.	Protein 88 g. Fat 68 g. Sugars 180 g. (20% dextrin)	94	Protein 54 g. Fat 61·5 g. Sugars 159 g. (40% dextrin)	84
C.L.	Protein 89 g. Fat 65 g. Sugars 189 g. (20% dextrin)	84	Protein 68 g. Fat 66·5 g. Sugars 208 g. (50% dextrin)	75·5
C.I.	Protein 104 g. Fat 57 g. Sugars 200 g. (20% dextrin)	88·5	Protein 66 g. Fat 67 g. Sugars 208 g. (50% dextrin)	69
J.R.	Protein 77 g. Fat 49·5 g. Sugars 185 g. (20% dextrin)	92	Protein 77 g. Fat 40·5 g. Sugars 175 g. (26% dextrin)	70
	Average ..	90		75

* Working with grants from the Sebag-Montefiore Fund and the Cheyne Hospital for Children Research Fund.

reliability, and therefore each balance was carried out over two consecutive periods of four days, the results being totalled to give an eight-day figure. The investigation was performed on four coeliac children, and the results are set out in table 1.

The first three cases are strictly comparable to each other, as at the completion of the balance on the first diet the high dextrin diet was started, and the second balance was carried out a month later. In the fourth case the first balance was conducted in July, 1948. The starch-free diet was then maintained, to the child's advantage, until the latter half of October, 1948, when it was changed to one containing 45 g. of starch. The fat absorption thereupon fell to 83 per cent. On November 12 the starch was removed from the diet and was replaced by an equal amount of dextrin, the 'dextrin balance' being started on November 22. The introduction of starch not only depressed the fat absorption, but was accompanied by a slight loss of weight and a setback in temperament, and it may be that these adverse effects were still operative at the time of the balance on the dextrin diet.

It will be seen that a high content of dextrin in the diet produced much the same effect in lowering the absorption of fat as has been previously reported to occur when starch was given. In addition the children became capricious and difficult to feed, and more irritable. For these reasons the high dextrin diets were abandoned because they proved to be just as unsuited to coeliac children as diets containing starch.

Dietary Starch and Fat Absorption in Pancreatic Fibrosis

The demonstration that starch in the diet of coeliac children depresses their capacity to absorb fat raises the problem of whether this is peculiar to coeliac children or applies also to other forms of steatorrhoea. In pancreatic fibrosis we have another disease of childhood which surpasses even coeliac disease in the severity and persistence of its steatorrhoea, and it was therefore decided to repeat on a group of four children suffering from pancreatic fibrosis the fat balance experiments that had previously been carried out on coeliac children.

The methods have been already described (Sheldon, 1949) and therefore need not be repeated here. The fat balances were carried out over two consecutive four-day periods, the results being totalled to give an eight-day balance. The first three children underwent a fat balance while receiving a starch-containing diet, and were then changed to a starch-free diet, and after an interval of twelve, fourteen, and nine days respectively their fat balance was repeated while they were on the second diet. The experiment on the fourth child was reversed, beginning with a fat balance during a starch-free diet, and then changing to a starch-containing diet, the second balance beginning eight days after the change of diet.

Throughout the tests none of the children received pancreatin.

The diagnosis of fibro-cystic disease of the pancreas in each child was based not only upon the

TABLE 2

RESULTS OF FAT BALANCE INVESTIGATIONS ON FOUR CHILDREN WITH PANCREATIC FIBROSIS

		Starch-containing Diet		Starch-free Diet	
Case	Age (in years)	Diet	Percentage Fat Absorption (8-day period)	Diet	Percentage Fat Absorption (8-day period)
D.C.	10	Protein 42 g. Fat 50 g. Sugars 65 g. Starch 111 g.	38	Protein 80 g. Fat 50 g. Sugars 135 g. No starch	32
A.F.	1½	Protein 48 g. Fat 59 g. Sugars 57 g. Starch 43 g.	45	Protein 61 g. Fat 76 g. Sugars 176 g. No starch	44
A.T.	4½	Protein 44 g. Fat 58 g. Sugars 123 g. Starch 99 g.	76	Protein 52 g. Fat 62 g. Sugars 142 g. No starch	81
A.H.	6½	Protein 73 g. Fat 80 g. Sugars 61 g. Starch 114 g.	38	Protein 74 g. Fat 79 g. Sugars 175 g. No starch	37
		Average ..	49·25		48·5

classical clinical picture, in which the nutritional calamity resulting from the pancreatic disorder was accompanied by chronic suppuration in the lungs, but also by demonstrating the complete absence of tryptic activity in the duodenal juices. On one of the children Dr. Payne kindly performed blood amino-nitrogen curves after meals of casein and casein hydrolysate, obtaining results that have been described by West et al. (1946) as typical of this disease.

The results of the investigation are set out in table 2. The averaged results of the four children indicate that fat absorption is considerably lower in pancreatic fibrosis than in coeliac disease, and the presence or absence of starch in the diet makes no appreciable difference to the level of fat absorption. Thus with starch in the diet the fat absorption averaged 49·25 per cent, and with no starch in the diet the fat absorption averaged 48·5 per cent. It would therefore appear that whilst in coeliac disease the presence of starch in the diet lowers the capacity for fat absorption, this is not true of all forms of steatorrhoea; it does not apply to the steatorrhoea that occurs in pancreatic fibrosis.

Chylomicron Counts

The older view of the physiology of fat absorption, namely that all fat has to be digested to fatty acids and glycerol before being absorbed into the lacteal system has been challenged by Frazer (1943). He has shown that a proportion of the dietary fat is finely emulsified in the upper intestine, and is absorbed as particles of fat into the lacteals, whence it is carried via the systemic circulation to the various fat depots in the body. The fat that escapes emulsification is digested to fatty acid and glycerol, and as such is absorbed into the portal system, to pass direct to the liver. With Stewart (1937), he has described a technique by which the finely emulsified fat particles in the serum can be counted. If a count is made on a fasting person, and then repeated at half-hourly intervals for three or four hours after a fatty meal, a lipaemia becomes apparent an hour after the meal, and reaches a maximum after two to three hours. By plotting these counts, a chylomicron curve indicative of particulate fat absorption is obtained. The method is similar to that used in arriving at a blood sugar curve after a meal of glucose, but differs in one important respect, for glucose after absorption into the portal system has to traverse the liver before reaching the systemic circulation, whereas particulate fat passes directly from the intestine into the lacteals, thoracic duct, and systemic circulation, and so avoids the liver.

The fat balances on coeliac children, to which reference has already been made, demonstrated a deficiency in fat absorption. By means of chylomicron curves, it was hoped to ascertain whether particulate fat absorption was defective, for were this not the case, the implication would be that coeliac children fail to absorb fat entirely at the expense of fat digestion and its absorption as fatty acid and glycerol. Our results show that in active coeliac disease (before recovery has set in) the chylomicron curve tends to be flat, indicating that defective particulate fat absorption accounts, at any rate in part, for the low fat balances. This accords with the statement of Frazer (1946) that patients suffering from idiopathic steatorrhoea (non-tropical sprue), who absorb only some 70 per cent. of their dietary fat, do so without any apparent lipaemia as judged by chylomicron curves.

We have no means of showing whether the digestion of fat and the absorption of fatty acid and glycerol is also diminished, and therefore whether both routes of absorption of fat are reduced in coeliac children. We have, however, been able to confirm the finding of Farber et al. (1943), that the production of lipase in the duodenal contents of coeliac children is normal, and there is no reason to suppose that the action of this enzyme is defective.

The chylomicron counts have been performed by one of us (A.M.), following the technique described by Frazer and Stewart. The children received no meal after midnight. Next morning a fasting sample of blood was withdrawn from a finger, and a meal of butter, 1 g. per kg. body-weight, was then given, further blood samples being taken at half-hourly intervals for three or three and a half hours. The serum obtained from centrifuging the samples was examined under dark ground illumination, and the bright fat particles (of 0·5μ diameter) in a 1/12 field were counted. Four counts were made on each specimen, and from these an average figure was obtained.

The results are shown in figs. 1-3. Fig. 1 shows

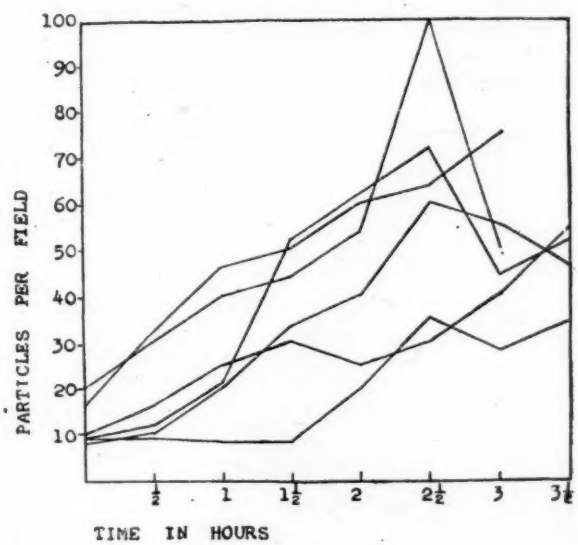

FIG. 1—Controls.

the curves obtained from six children between two and eight years old, whose digestion and stools were considered to be normal. These children acted as

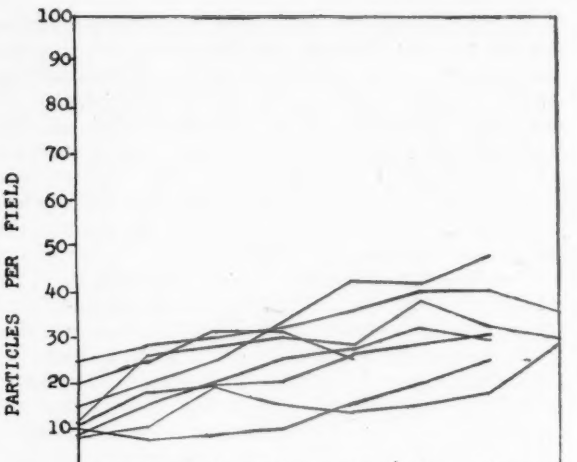

FIG. 2—Before recovery.

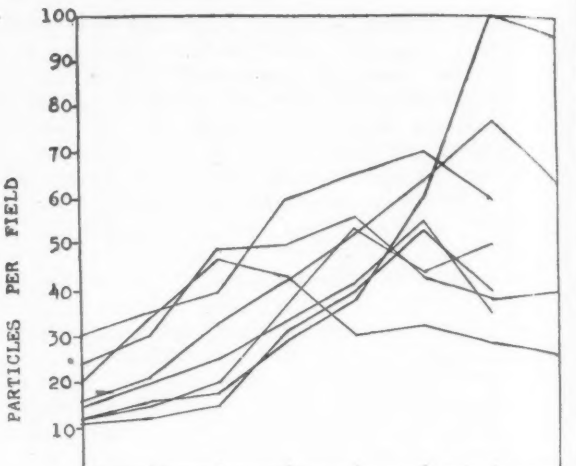

FIG. 3—During recovery.

controls. Their chylomicron curves show a rise in the number of fat particles per field in the first hour, the rise reaching a maximum in two to three hours. The maximum rise from the fasting level in these children averaged fifty-three particles per field.

Chylomicron curves have also been obtained from sixteen children with coeliac disease. Fig. 2 shows the curves from eight of these children, shortly after their admission to hospital, and before any clinical improvement had become apparent. It is evident that these curves, viewed as a whole, are much flatter than those of the control children, and the maximum rise from the fasting level in this group averaged twenty particles per field.

The remaining eight coeliac children were examined some weeks after admission to hospital, when their clinical state was steadily improving under the influence of a starch-free diet. Their chylomicron curves are shown in fig. 3, and it can be seen that in the aggregate they differ considerably from those in fig. 2, but approximate to the normal control curves in fig. 1. The maximum rise from the fasting level in these children averaged forty-three particles per field.

In view of the improvement in fat absorption which coeliac children experience when starch is removed from the diet, it was natural to enquire whether the chylomicron curves were affected if, immediately before the investigation, the children had been receiving a starch-containing or a starch-free diet. Figs. 4 and 5 show the effect of regrouping the curves from figs. 2 and 3 according to whether

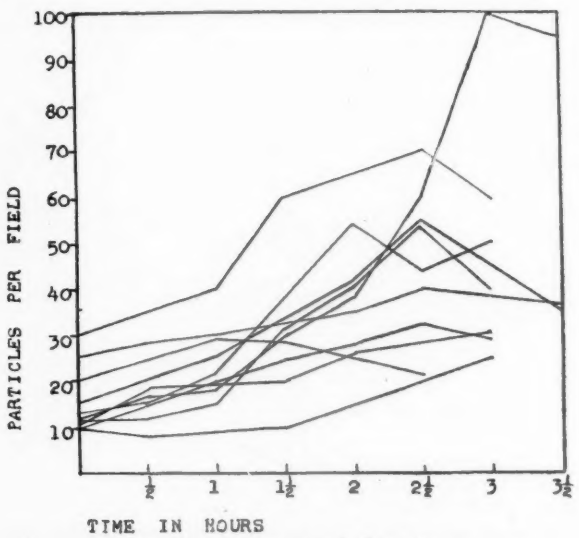

FIG. 4—During starch-free diet.

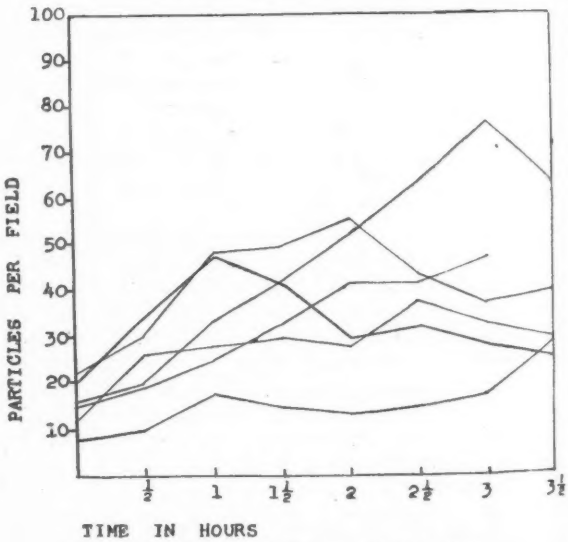

FIG. 5—During starch-containing diet.

the preceding diet contained starch or was starch-free. The maximum rise from the fasting level in figs. 4 and 5 were the same, averaging thirty-three particles per field, and the two sets of curves are roughly similar. Our results suggest that in coeliac children the chylomicron curve is influenced more by the stage of the illness than by the composition of the diet immediately preceding the test. When the disease is active, particulate fat absorption appears to be defective; clinical improvement is accompanied by improvement in particulate fat absorption.

It is of interest that these results accord with those obtained by Kellett (1932) who reported a similar investigation made on three children with coeliac disease.

Summary

In children with coeliac disease, a high content of dextrin in the diet (26 to 50 per cent. of the carbohydrate as dextrin) lowers the capacity to absorb fat much as does starch.

In children with pancreatic fibrosis, the presence or absence of starch in the diet does not appear to affect the capacity to absorb fat. In this respect, pancreatic fibrosis is in contrast to coeliac disease.

Chylomicron counts in coeliac disease indicate that defective absorption of particulate fat accounts, at any rate in part, for the failure to absorb fat adequately. Clinical improvement is accompanied by improvement in particulate fat absorption.

We wish to express our thanks to Dr. Payne and the technical staff of the Biochemical Laboratory at the Hospital for Sick Children, Great Ormond Street, for carrying out the faecal fat analyses. We wish also to thank those members of the nursing staff who were concerned with the day to day management of the fat balances.

REFERENCES

Farber, S., Shwachman, H., and Maddock, C. L. (1943). *J. clin. Invest.*, **22,** 827.
Frazer, A. C. (1943). *J. Physiol.*, **102,** 306.
—— (1946). *Schweiz. med. Wsch.*, **76,** 903.
——, and Stewart, H. C. (1937). *J. Physiol.*, **90,** 18.
Kellett, C. E. (1932). *Lancet*, **2,** 1270.
Sheldon, W. (1948). *Brit. med. J.*, **2,** 594.
—— (1949). *Arch. Dis. Child.*, **24,** 81.
West, C. D., Wilson, J. L., and Eyles, R. (1946). *Amer. J. Dis. Child.*, **72,** 251.

PROTEIN REQUIREMENTS OF INFANTS*

2. MARASMUS

BY

W. F. YOUNG, M.D., D.C.H., E. A. BISHOP, M.B., B.S., D.C.H., EVELYN M. HICKMAN, M.Sc., Ph.D., and YVONNE J. WILLIAMS, M.D.

(From the Children's Hospital and Department of Paediatrics and Child Health, University of Birmingham)

Failure to gain or actual loss of weight is a common condition in young infants which has been a subject of discussion for centuries, and in the past there was a tendency to regard wasting as a clinical entity. This conception is entirely wrong (Parsons, 1924); it is but a symptom of some underlying condition and is in this respect comparable with other common symptoms such as vomiting, convulsions, and diarrhoea, none of which is regarded as a disease sui generis. The causes of severe wasting may be classified under two main headings, (a) insufficient food, and (b) presence of infection. Insufficient food may be due to quantitative or qualitative defects in the diet or it may be the result of impaired absorption from the alimentary tract due to disease or diarrhoea. It may also be due to insufficient food reaching the intestine, as in abnormal conditions of the oesophagus or of the stomach, for example, pyloric stenosis. It is difficult in some cases to separate lack of food from the presence of infection as the cause of wasting, because vomiting and diarrhoea and intolerance of food may be the result of infection and so introduce the starvation factor. Conversely, the infant who is not receiving adequate food is more liable to infection than the one whose nutrition is normal. In treating states of malnutrition it is always necessary to discover the underlying cause, for unless this is removed, the measures designed to arrest the progress of wasting will probably fail.

Recent studies have shown that gross protein depletion may occur in wasted subjects. Starvation deprives the body of the protein which is normally retained by growing infants, and it may be assumed that infection and injury accelerate protein metabolism in infants as has been described in adult man and in animals (Cuthbertson, 1944; Himsworth, 1946), causing the well recognized association between infection and marasmic states. The losses due to accelerated protein metabolism may be severe, and it is thus easy to understand why an infant may 'fall away' during the course of a week or two. Furthermore, mobilization of tissue protein seems to be accelerated when the body-weight falls below 80 per cent. of its expected level in infants, and there is a rise in the basal metabolic rate (Talbot, 1921; Fleming, 1921). Fleming has suggested that in the first stages of atrophy the loss of weight is taking place mainly at the expense of metabolically inactive tissue (fat) but that as it advances there is a greater wastage of metabolically active tissue (muscle). A still later stage of wasting in infants (below 70 per cent. of their expected weight) is associated with a fall in the basal metabolic rate. The functions of the respiratory and of the cardiovascular systems may then begin to fail with slowing of the pulse and respiration rate and a subnormal temperature. The patient's condition is critical and a return to normal function is seldom achieved. There is, therefore, a very small margin of safety in treating infants who have wasted to 80 per cent. of their expected weight, and every effort must be made to improve their condition or at least to prevent its deterioration. Tolerance for food is low, and the dilemma may arise of choosing between the risks of a period of semi-starvation while the diet is being built up slowly, and those of over-feeding with the consequent development of diarrhoea and vomiting. The accepted practice is to begin with a low intake of total calories supplying only the maintenance requirements of about 25-35 calories/lb./day (50-70/kg./day) and to be guided by the progress of the patient in increasing them to his full requirements for gaining weight. The fluid intake is maintained at $2\frac{1}{2}$-3 oz./lb./day (150-180 ml./kg./day) and the calorie intake is increased by strengthening the feeds. The intake of fat is usually low (concentrations below 2 per cent.) unless human milk is being given, because experience has shown that fat is badly tolerated, but carbohydrate is allowed in high concentrations (7-12 per cent.). The protein intake varies. It is often recommended that the amount of protein

* Part of a report prepared for the Medical Research Council's Committee on the Protein Requirements of Infants. The first part of this report was published in September, 1949.

contained in undiluted cows' milk should be given, but that tolerance to this amount of curd should be acquired by strengthening the milk and water mixtures gradually. In the past this feeding method has given good results in a majority of cases at the Children's Hospital, Birmingham. A number of infants, however, have continued to lose weight and have died before their nutrition had begun to improve; often pneumonia was the terminal event. The prognosis for such patients has changed since sulphonamide drugs and penicillin have been available. Nevertheless, anxiety about the nutrition of babies admitted to hospital with very severe degrees of wasting has continued, lest they should succumb to infection or to a failure of metabolism before improvement in their nutrition has been achieved.

When preparations of protein digests became available it was appreciated that they might be used to provide an easily assimilable food and to augment the protein intake of marasmic infants at the beginning of their treatment. Young infants suffering from malnutrition or infection may have hypochlorhydria (Marriott and Davidson, 1923; Parsons, 1924), and relative pancreatic insufficiency (Andersen, 1942). It is, therefore, rational to give them hydrolysed protein which can be absorbed by the alimentary tract without much digestive activity. Furthermore, the mixture of polypeptides and amino-acids of which the digests are composed is freely soluble and no curd is formed in the stomach. Information concerning the phase of recovery from malnutrition in infancy is scanty, and the maximum rate at which repair can be achieved has not been studied in relation to dietary intake. The protein intake should be high enough to allow for nitrogen retention to proceed at a greater rate than it does during periods of normal growth and, in planning the feeds to be used in this investigation, it has been considered that 4-6 g. protein/kg./day would probably be adequate in this respect. Preparations of casein hydrolysate for oral administration became available in 1944 and a preliminary trial of three of these was arranged forthwith. Amounts to increase the concentration of protein by 1 per cent. or 2 per cent. were added to the cows' milk mixture or to the expressed breast milk which was being used to feed twenty-five infants. Most of the infants took the feeds well without disturbance of alimentary function. Some had four to five bowel movements a day and the stools were somewhat relaxed, but the patients continued to thrive and to gain weight satisfactorily without any change in the composition of the feeds. Since hydrolysed casein was found to be well tolerated by infants, it was planned to use it systematically for feeding marasmic babies. One of the preparations used in the trial, 'casydrol',* was used throughout the subsequent investigations.

Feeds for Marasmic Infants

The composition of the cows' milk feeds which have been used is shown in table 1. They have been arranged in stages so that the diet can be changed gradually from a milk mixture containing part of the protein as hydrolysed casein to one consisting of undiluted cows' milk. The composition with regard to fat and carbohydrate has also been graded. If expressed human milk was being used 1 per cent. or 2 per cent. of hydrolysed casein was added to increase the total concentration of protein to 2½-3½ per cent. The cows' milk feeds were acidified in order to augment the acid in the stomach of infants likely to have hypochlorhydria.

* 'Casydrol' is prepared by Genatosan Ltd., but it should be noted that the manufacturers have changed the composition of 'casydrol' so that it is no longer 100 per cent. hydrolysed casein.

TABLE 1

COMPOSITION OF FEEDS USED FOR MARASMIC INFANTS

	Milk Formulae	(%)			Calories and Protein (g.) supplied (2½-3 oz./lb./day)	
		Protein	Carbo-hydrate	Fat	Calories/kg. bodyweight	Total Protein/kg. bodyweight (g.)
Stage I Calories/oz.=17	Lactic acid milk 4 oz. Water 8 oz. 'Dextri-Maltose' 6 dr. Casein hydrolysate 9·6 g.	3·7	8·4	1·3	92–110	5·6–6·7
Stage II Calories/oz.=20	Lactic acid milk 6 oz. Water 6 oz. 'Dextri-Maltose' 6 dr. Casein hydrolysate 9·6 g.	4·2	9·1	2·0	107–129	6·3–7·6
Stage III Calories/oz.=20	Half-cream 'Lacidac' 12 dr. Water 12 oz. Sugar 3 dr.	3·7	8·7	2·0	106–127	5·6–6·7

Thrush and other organisms are often present in the pharynx, oesophagus and stomach, and Esch. coli is sometimes prevalent in the stomach and upper bowel of infants who are suffering from hypochlorhydria. The growth of all these organisms may be inhibited by an acid medium. The stronger feed, Stage II, was introduced as soon as toleration of the weaker mixture had been established in order to give the higher caloric intake of 20 cals./oz. (see table 1). The substitution of the Stage III feed, in which whole protein entirely replaces hydrolysed casein, was delayed until a considerable amount of progress had been made, judged by a regular gain in weight, but it was always made before the patients were discharged from hospital. This last change in the feed was made gradually over a period of several days, and if the stools became bulky the transition was delayed.

Vitamin supplements were given as follows:

' Tab. benerva co. ' 1 daily	aneurin (B1)	1 mg.
	riboflavine	1 mg.
	nicotinic acid amide	15 mg.
Ascorbic acid 50 mg. daily	Vitamin A	4,000-7,000 units.
' Adexolin ' m. 6-10 daily	Vitamin D	700-1,200 units.

Iron supplements were given to four infants, two of whom were premature, but they were not used as a rule.

If infection had been present or if the patient did not begin to gain weight, fresh blood or plasma transfusions were sometimes given during the first week or two of treatment.

Subjects for the Investigation

Observations were made on seventy-nine young infants between two and seventeen weeks of age who weighed 80 per cent. or less of their expected weight at the beginning of treatment. Twenty-one of these were excluded from the final analysis of results for reasons which will be given later. The clinical material for the main investigation therefore consisted of fifty-eight infants, and these were divided broadly into infants suffering from pyloric stenosis (insufficient food), and infants suffering from marasmus due to other causes (chiefly infection). Each of these divisions contained some infants who made steady progress and others whose progress was retarded by complications, such as infection. The infants were therefore finally divided into the following four groups.

Group No.	Condition	Progress	No. of cases
1	Pyloric stenosis on admission ..	Uncomplicated	20
2	„ „ „ ..	Complicated	15
3	Marasmus due to other causes ..	Uncomplicated	6
4	„ „ „ ..	Complicated	17

Four of the infants (two in Group 2 and two in Group 4) in our investigation weighed between 4½ and 5 lb. at birth and must be regarded as having been born prematurely. Consequently, their progress should not be compared with that of infants born at term, and the observations made on these babies have been recorded (P) on the figures in order to distinguish them. There were a number of other infants who weighed between 5 and 6 lb. at birth, but the observations made on them have been assessed together with those of babies with

TABLE 2

METHOD OF GRADING STRENGTH OF FEEDS AFTER OPERATION FOR PYLORIC STENOSIS

Period after operation (hours)	Composition of feed		Feeding intervals	Volume of feed per 24 hours
	Milk formula (Stage II in Table 1)	5% ' Dextri-Maltose ' (± NaCl)		
0–12	4 drams	4 drams	Two-hourly × 12	12¾ oz.
12–24	5 drams	4 drams		
24–36	6 drams	4 drams	Two-hourly × 12	16½ oz.
36–48	8 drams	4 drams		
48–60	10 drams	4 drams	Two-hourly × 11	20½ oz.
60–72	12 drams	4 drams		
4th day	2 oz.	—	Two-hourly × 10	20 oz.
5th day	2½ oz.	—	Three-hourly × 8	20 oz.
6th day	3 oz.	—	Three-hourly × 7	21 oz.

higher birthweights, since the development of malnutrition in our patients was judged to have been little affected by variations in their size at birth.

Pyloric stenosis was treated surgically, and the course of infants (Groups 1 and 2) during the post-operative period is described. A special feeding schedule (see table 2) was arranged for them by which a quick transition was made to Stage II feeds (see table 1). By following this schedule the patients received the undiluted milk mixture (Stage II) on the fourth post-operative day. More caution was exercised in feeding a few of the very ill babies, but all cases were being given the undiluted feed by the end of the fifth day after operation. The volume of the feeds was adjusted to supply 150 ml./kg. body-weight (2½ oz./lb. body-weight) daily by the end of the first week. Salt was added to the feeds to supply about 1·0 g. NaCl daily until the silver nitrate test for chlorides in the urine gave a flocculent deposit. The infants whose marasmus was due to causes other than pyloric stenosis (Groups 3 and 4) were treated according to their special needs, and many of them were given sulphadiazine and penicillin to combat infection.

The other twenty-one marasmic infants who received casein hydrolysate were excluded from the main analysis of the results for the following reasons. Six infants had casein hydrolysate added to human milk instead of to the lactic acid milk mixtures which were used for the majority of the infants; good results were obtained. In eleven cases the feeding schedule was not followed systematically, but only once was casein hydrolysate discontinued because it was suspected to be the cause of vomiting. The remaining four omissions were infants found at necropsy to have been suffering from a congenital abnormality, namely, hydrocephalus, stenosis of the lower end of the oesophagus, and cystic fibrosis of the pancreas (two cases), which had caused persistent failure to thrive.

Intake of Food

The average intake of food for the cases in Groups 1 and 3 during the early weeks of treatment is shown in table 3, but the intakes of patients in Groups 2 and 4 have not been averaged because they were more variable. Although the intake was often reduced for a short period in a patient suffering from infection, it was soon increased so that most of the infants in Groups 2 and 4 were receiving similar amounts to those in Groups 1 and 3 for the greater part of their course. Table 3 shows that during the second week after operation the average daily intake for patients in Group 1 reached 122 calories and 6·8 g. protein/kg./day and that during subsequent weeks the same intake was maintained. The average intake of the patients in Group 3 was somewhat greater than this after the third week. The casein hydrolysate feeds were replaced earlier by stronger milk mixtures (Stage III) for the patients in Groups 1 and 3 (two to three weeks) than for those in Groups 2 and 4 (three to twelve weeks) whose progress was retarded by complications.

Assessment of Wasting and Progress in Response to Treatment

The degree of wasting and progress towards recovery were assessed by comparing the patient's weight with that of healthy infants of the same age. Statistical studies of weight throughout infancy have not been made in Great Britain, but data for the white races in the U.S.A. are available from the results of a study which was made in Iowa (Jackson and Kelly, 1945). The average weight for male and female infants at the 50th percentile and one standard deviation below and above it (the 16th and 84th percentiles respectively) on the Iowa weight curves have been taken as the standard range for infants of different ages in the present investigation.

TABLE 3

AVERAGE DAILY CALORIE AND PROTEIN INTAKE OF INFANTS IN GROUPS 1 AND 3 DURING FIRST SIX WEEKS OF TREATMENT

Weeks	First week		Second week		Third week		Fourth week		Fifth week		Sixth week	
Groups	1	3	1	3	1	3	1	3	1	3	1	3
No. of Cases	20	6	20	6	19	6	15	5	9	4	8	3
Calorie intake/ kg. bodyweight/day	84	100	122	124	121	126	122	136	125	134	123	134
Total Calorie intake/day	257	287	400	384	424	412	452	475	472	486	512	497
Protein intake/ kg. bodyweight/day	3·88 g.	4·90 g.	6·84 g.	7·40 g.	6·12 g.	7·40 g.	6·06 g.	7·72 g.	6·08 g.	7·40 g.	6·08 g.	6·84 g.
Total Protein intake/day	12·6 g.	14·4 g.	22·6 g.	22·6 g.	21·5 g.	24·4 g.	22·5 g.	28·0 g.	23·2 g.	26·8 g.	25· 3g.	24·6 g.

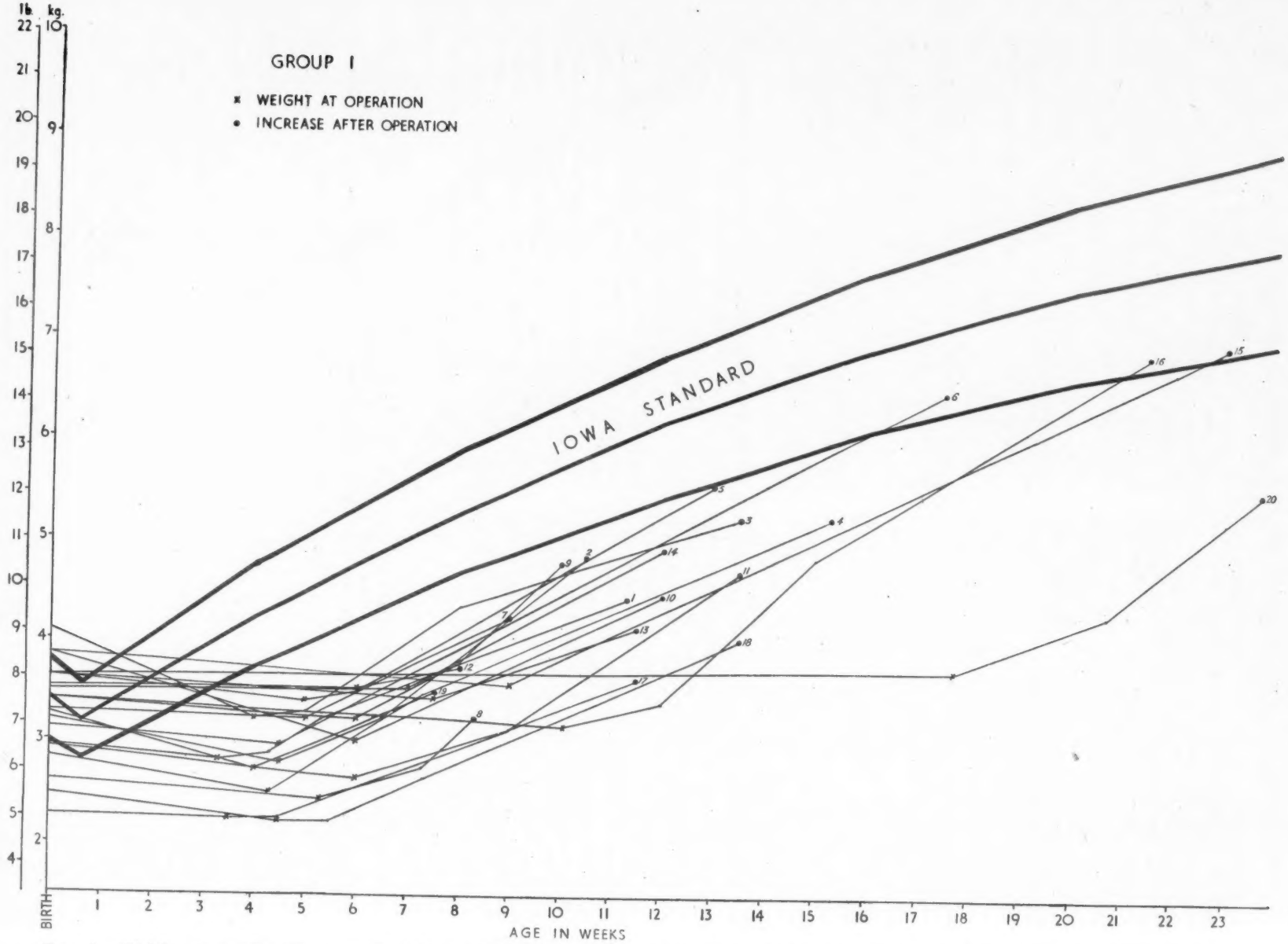

FIG. 1.—Weight curves of twenty marasmic infants, admitted with pyloric stenosis, compared with Iowa standard weight curves of normal infants.

AGE IN WEEKS

FIG. 1.—Weight curves of twenty marasmic infants, admitted with pyloric stenosis, compared with Iowa standard weight curves of normal infants.

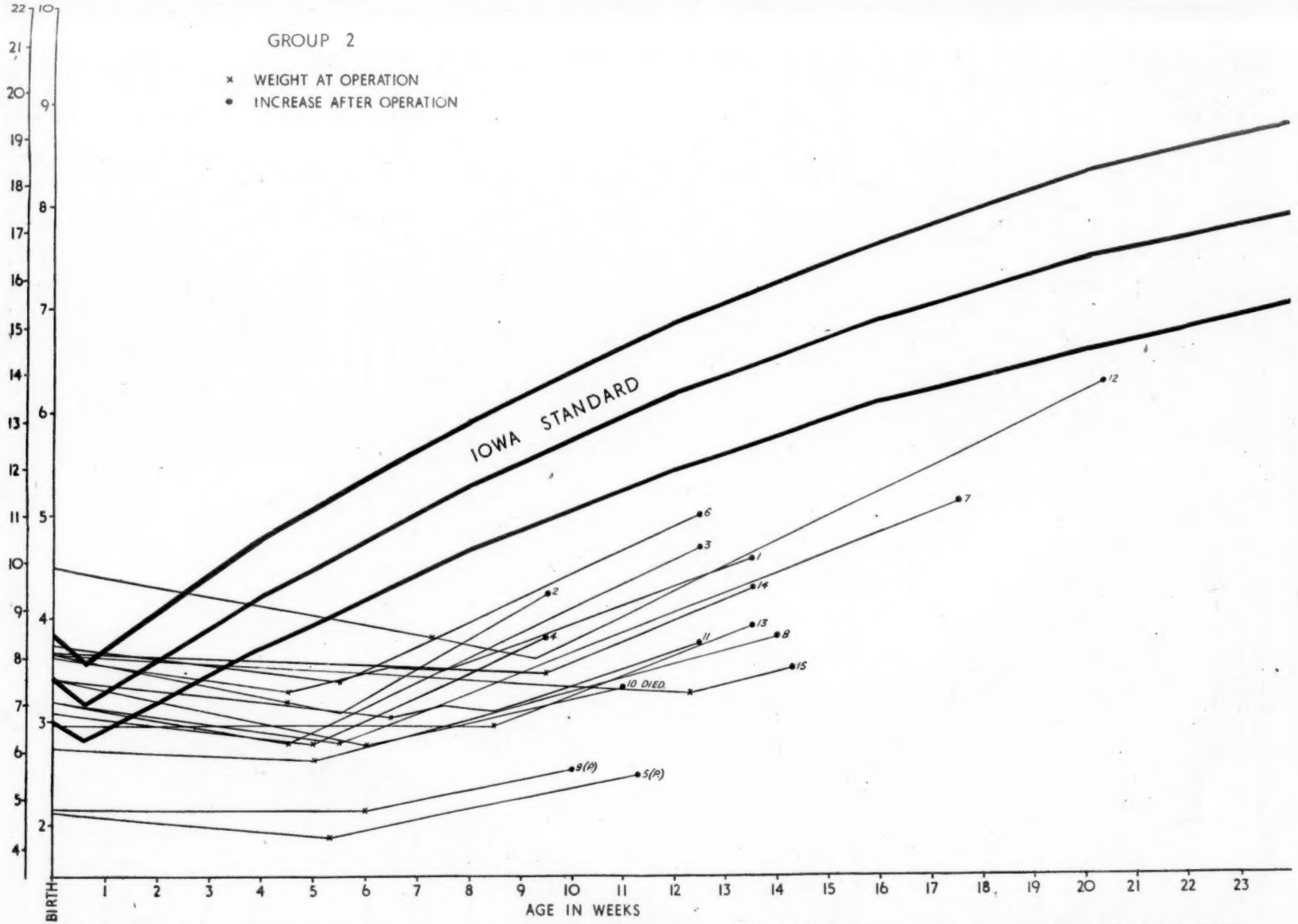

FIG. 2.—Weight curves of fifteen marasmic infants, admitted with pyloric stenosis, compared with Iowa standard weight curves of normal infants.

The degree of initial wasting in each patient, however, has been assessed roughly by taking the weight on admission (or after rehydration if dehydration were present) and comparing it with the weight at birth

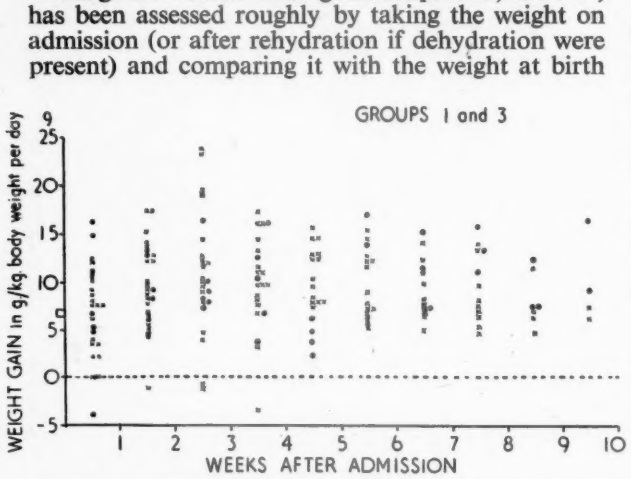

FIG. 3.—Scatter diagram of weight gains per kg. body weight per day of twenty-six infants (Groups 1 and 3).

plus 5 oz. for each week of age, that is, the expected weight. The clinical signs of malnutrition were usually in agreement with the assessment made on weight; in a few cases they were not, and such infants were omitted from the investigation. An underweight infant must gain weight faster than the normal infant in order to catch up and reach the normal range of weight levels. Individual progress was therefore gauged by the rapidity with which this was achieved.

Fig. 1 is a comparison between the Iowa standards and the weight curves from birth of the twenty marasmic infants suffering from pyloric stenosis who made straightforward progress after operation (Group 1). The weight of the patient at operation was always taken after dehydration had been corrected. Later, points from the weekly weight records have been graphed only at times when there was a change in rate and therefore in the slope of the line. It can be seen that pyloric obstruction was treated at an interval after birth varying between three and seventeen weeks and that many of the infants had lost, and none of them had gained, weight during this time. Subsequently, there was a considerable variation in the rate at which weight was gained, but in every case a steady increase was achieved. It will be noticed that the slope of the line (representing the rate) is often steeper than the slope of the standard curves and that the weight then begins to approach the normal. At three months of age many of the babies were still far below the standard although several weeks had usually elapsed since the time of their operation. Most of them, however, were by then gaining weight at a rate which, if continued, would enable them to reach the normal range within the next few weeks. No. 20 was an exceptional case. He had become progressively wasted until, at seventeen weeks, pyloric stenosis was diagnosed, and by this time he weighed only 50 per cent. of his expected weight by the Iowa standard. Operation was followed by the usual feeding regime for marasmic infants and excellent progress was made. At twenty-three weeks he was nearing the normal range.

Fig. 2 shows the weight curves of the fifteen infants with pyloric stenosis whose progress was retarded by infection (Group 2). In general, the course of these infants was slower than that of the patients in Group 1, but it was usually retarded for a time only, later the rate of gain becoming similar to that of the uncomplicated cases. This was to be expected since infections were often controlled within a week or two. The intake of food had sometimes to be curtailed for these babies, but the calorie intake was

TABLE 4
VARIATION IN AMOUNT OF WEIGHT GAINED PER WEEK BY INFANTS IN GROUPS 1 AND 3

	Weeks	1	2	3	4	5	6
Group 1	Average weight Gain (g./week)	153	227	275	266	303	293
	Range ..	0 to +270	−28 to +455	−28 to +540	−71 to +511	+198 to +498	+128 to +455
	No. of cases ..	20	20	19	17	14	13
Group 3	Average Weight Gain (g./week)	144	196	222	238	110	280
	Range ..	−85 to +325	+85 to +270	+184 to +312	+99 to +341	+57 to +142	+156 to +425
	No. of cases ..	6	6	6	5	4	4

never reduced to 'maintenance' levels, and was increased by giving Stage II feed as soon as possible. Many of the infants continued to gain weight despite the fact that severe infections were present. One infant (No. 10) died six weeks after operation from epidemic gastro-enteritis contracted three days previously. His course after operation had been complicated by persistent vomiting, and at necropsy he was found to have a healed cerebral birth injury which might have caused this symptom and accounted for his slow progress.

Fig. 3 shows the weight gains (as g./kg./day) during each week, for the two groups of infants (1 and 3) who made straightforward progress. It will be seen that the range is wide, but that a large number of infants were gaining much more than the 7 g./kg. daily which is the average for healthy, full-term infants during the second and third months of life. The relatively higher rate of gain achieved by the marasmic infants is due partly to larger total weight gains (see fig. 1) but partly to their initially low weights. Since requirements of food are always prescribed on the basis of body-weight, however, the amount of weight which is being gained can best be related to the diet if it is expressed as g./kg./day. Fig. 3 shows that a gain of 15 g./kg./day was often achieved by patients who were fed according to the regime shown in tables 1 and 2. Amounts of nitrogen equivalent to 2-3 g. protein/kg./day must have been retained by these infants (weight gain = $\frac{1}{6}$-$\frac{1}{5}$ protein). Hence, allowing for a 50 per cent. utilization, their diet (containing about 6 g. protein/kg./day) was probably sufficient for their needs. The high content of minerals in the diet may also have contributed to these results.

Fig. 4 shows the cumulative gain in weight of the infants during the early weeks of their treatment. The weight gains of the individuals in Groups 2 and 4 (complicated cases) have been graphed to compare with the average gains of those in Groups 1 and 3 (uncomplicated cases). The range for change in weight and the average gains each week for Groups 1 and 3 are given in table 4. It can be seen that on an average the infants in Group 1 were gaining about 275 g. (10 oz.) per week from the second to the sixth week and that many were gaining considerably more than this, the maximum gain being 540 g. per week (19 oz.). The rate of gain shown in the Iowa curves during a similar age period (sixth-twelfth week) is about 235 g. per week, but healthy infants seldom gain amounts which greatly exceed this. Fig. 4 shows that the progress of some of the infants with complications (Groups 2 and 4) was similar to that of the infants in Groups 1 and 3; others gained slowly for a week or two, but later there was an increase in the rate. A few infants lost weight and, later, gained slowly for several weeks. One infant in Group 4 (No. 16) died of severe infection contracted during the neonatal period. Nevertheless, the nutrition of many of the infants in these groups was well maintained at times when infection might have been expected to produce a steady downhill course.

Serum Protein and Haemoglobin Levels

The amounts of serum protein and haemoglobin have been found to fall in starvation and in protein depletion and to rise during periods of recovery in experimental animals (Weech, Goettsch, and Reeves, 1935; Weech, Wollstein, and Goettsch, 1937; Sabine and Schmidt, 1943; Chow, 1946) and in adult man (Mollison, 1946; Walters, Rossiter, and Lehmann, 1947). The changes in serum protein levels are due mainly to the albumin fraction. The blood volume also falls in starvation and rises in recovery and such variations in volume may mask an absolute decrease or increase in the amounts of total circulating protein and haemoglobin. Marriott (1920) and Utheim (1920) have found that the blood volume and the concentration of protein and of haemoglobin are often low in marasmic infants. Infection, if present, contributes to the production of low levels by depressing haemoglobin formation (Davidson and Fullerton, 1938; Vaughan, 1948) and plasma regeneration. Changes in the haemoglobin and serum protein levels cannot be used as a guide to the degree of depletion or to assess recovery in marasmic infants, since the normal range for both serum protein and haemoglobin levels is wide in infancy, and they are often affected by factors other than protein depletion, such as infection and changes in the blood volume.

When the present investigation was being planned it was decided to take samples of blood for serum protein and haemoglobin estimations at the outset of treatment and again at weekly intervals and to obtain them from scalp veins by venipuncture. Unfortunately it has not been possible to follow this programme systematically, but the blood of most of the patients has been examined on several occasions; exceptions were two infants in Group 1 and three infants in Group 4. The samples were usually obtained by scalp vein puncture but capillary blood from a heel-prick was occasionally used. The number of weekly levels from each case varied, depending upon the duration of in-patient treatment and upon the number of return visits. Since follow-up care usually extended over a longer period for the more severe cases, the levels for the later weeks of treatment may lie within a lower range than would have been the case if complete sampling had been achieved. A greater number of levels were estimated on the patients in Groups 2 and 4, whose progress was retarded, than on those in Groups 1 and 3 who made straightforward progress.

Serum was used for the protein estimations, haemolysed specimens being discarded. The total nitrogen was determined by micro-Kjeldahl digestion followed by nesslerization. Albumin nitrogen and non-protein nitrogen were estimated by the same method; the globulin was removed by precipitation with 22·2 per cent. sodium sulphate followed by filtration and the total protein was precipitated by

sodium tungstate and sulphuric acid. A correction was applied in calculating the total protein nitrogen and albumin nitrogen by subtracting the non-protein nitrogen. Since completing this investigation it has been found that the average of a series of results for total serum protein levels obtained by this method is lower, by approximately 0·3 g./100 ml., than the average of the same series of results obtained by the digestion of 0·1 ml. of serum followed by steam distillation and titration. Fortunately the same nesslerization technique has been employed to determine the serum protein levels in a series of normal infants (Poyner-Wall and Finch, 1949) and the results of this investigation have been used as a standard with which to compare the levels of our patients.

Haemoglobin was estimated in the Evelyn photoelectric colorimeter against a standard curve based on Van Slyke's oxygen capacity determination using the commonly accepted value of 1·34 ml. of oxygen/g. haemoglobin (100 per cent. = 13·8 g. haemoglobin, the Haldane standard 'normal' level at the time when this investigation was in progress). The haemoglobin levels of normal infants have not been estimated by the same technique, but Horan (1949) has used the Haldane method to estimate the haemoglobin levels of a series of normal infants in Birmingham matching them against a standard solution by direct vision. The results obtained by this investigator have therefore been used as a standard with which to compare the levels of our patients. The curve showing the average haemoglobin levels of artificially fed infants between one and five months of age lies about 10 per cent. higher than that obtained by Mackay (1933) for London infants using the same method for the estimations.

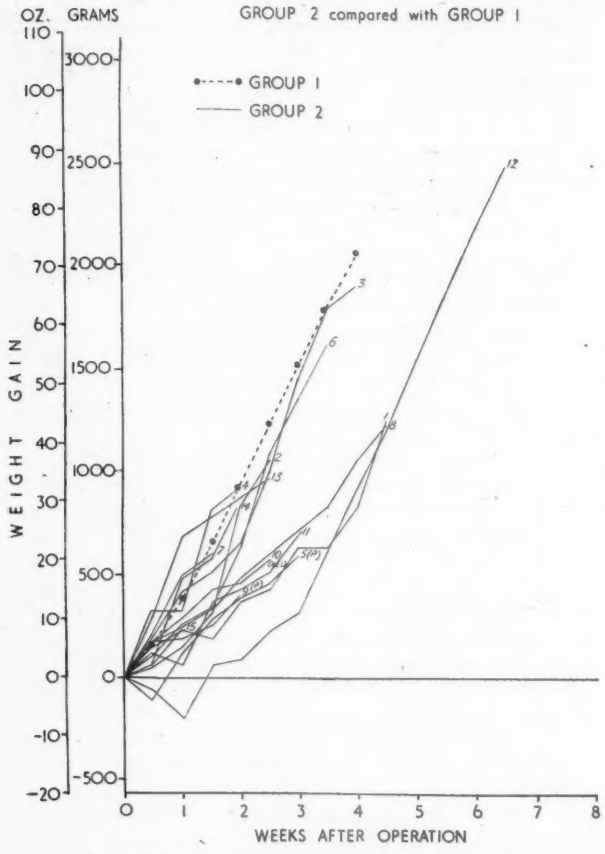

FIG. 4a.—Cumulative weight gains of fifteen infants (Group 2) admitted with pyloric stenosis (complicated course) compared with average gain of twenty infants (Group 1) making steady progress.

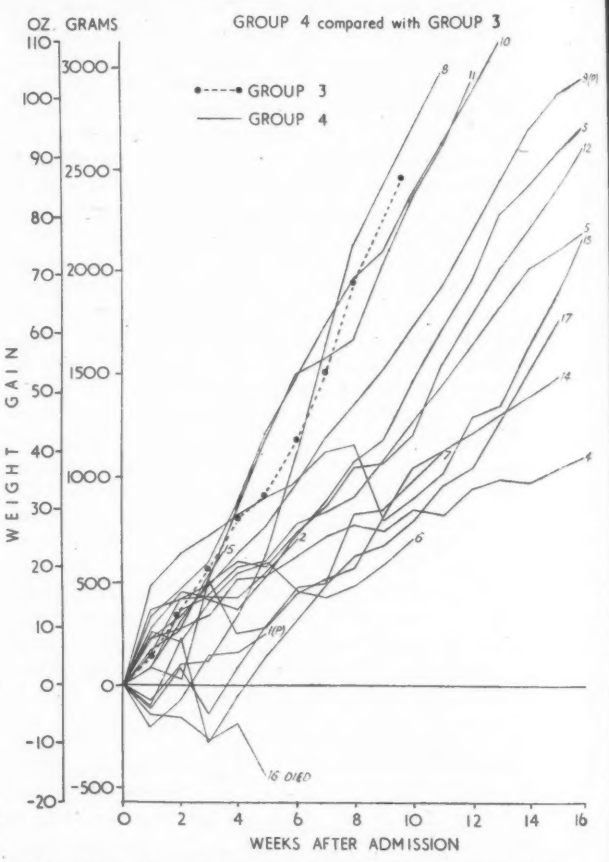

FIG. 4b.—Cumulative weight gains of seventeen infants (Group 4) suffering from marasmus associated with infection compared with average gain of six infants (Group 3) without infection.

Serum protein levels. Fig. 5 shows the serum protein levels of the four groups of infants compared with the average level for normal infants of similar ages, that is, one to five months (Poyner-Wall et al., 1949). The levels of the infants who made steady progress (Groups 1 and 3) have been graphed separately from those whose course was retarded by infection (Groups 2 and 4). Both sections of the

diagram show that during the first two weeks of treatment a larger number of the levels were below than were above the average line for normal full term infants. After four weeks, however, a greater proportion of the levels reached a value above the line for the infants in Groups 1 and 3, while they continued to be below it for those in Groups 2 and 4, whose progress was complicated by infection. The levels show a wide scatter and no close relationship was found between them and the severity of the wasting in the different patients.

The protein levels of our patients were higher than those for marasmic infants recorded by other workers (Utheim, 1920), and the uniformly high protein diet used in this investigation may account for this difference. Hypoproteinaemia was more often found amongst the group of marasmic infants who were the subjects for the preliminary tests with casein hydrolysate, and these patients were usually given much less protein than the infants in the later systematic investigation.

The results of serial estimations of the serum protein levels in individual infants often showed unexplained fluctuations from week to week. A pattern was discernible, however, in the recovery phase of many of the infants in Group 1, and it is shown in fig. 6. The initial serum protein concentrations within a few days of operation were found to be higher than those one to three weeks later, whereas subsequent values showed an increase. This sequence or part of it was found in fifteen out of the sixteen infants in Group 1 whose levels were estimated regularly. The same changes occurred in the levels of a number of the infants in the other groups but not so consistently. The cases within Group 1 were more alike clinically than were those in the other groups, and this may explain why the sequence of changes in their serum protein levels was more uniform. The pattern is similar to the one described during recovery from protein depletion in rats (Cannon, Humphreys, Wissler, and Frazier, 1944) and in adult man (Walters et al., 1947). It was then shown to be due to an initial rise in the blood volume which takes place at a faster rate than the increase in the amount of total circulating protein. The serum albumin levels obtained from the same samples of blood as were used for the total serum protein levels are also shown in fig. 6. It will be seen that they usually changed in the same direction as the total protein levels and that the changes in albumin were then mainly responsible for the fall and rise in the total concentrations.

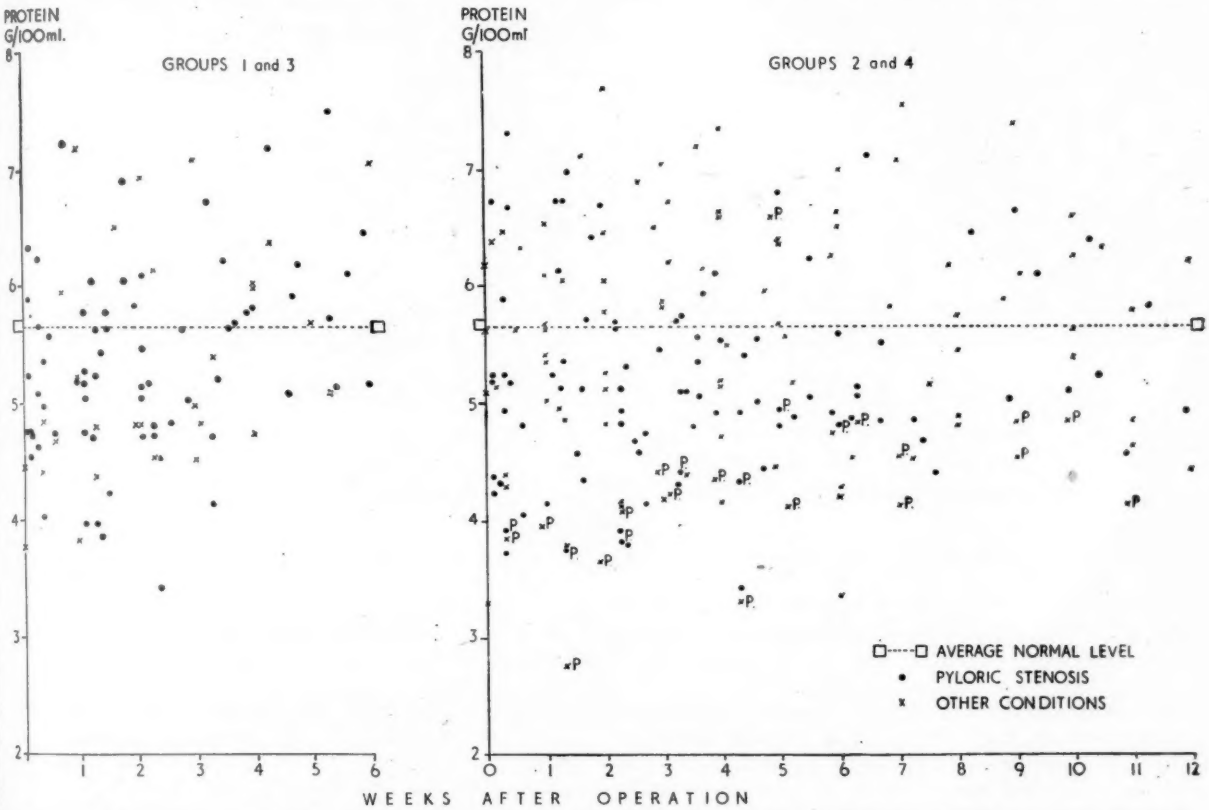

FIG. 5.—Serum protein levels of marasmic infants (a, Groups 1 and 3; b, Groups 2 and 4) compared with average serum protein levels of normal infants in same age group, 1-5 months (Poyner-Wall and Finch, 1949).

This was also found to be the case in animals and adults suffering from malnutrition (Weech et al., 1935; Rossiter, 1946). In some of our patients, however, the albumin concentration changed in the opposite direction from the total protein; no explanation is offered for these differences in the fractionation of albumin and globulin.

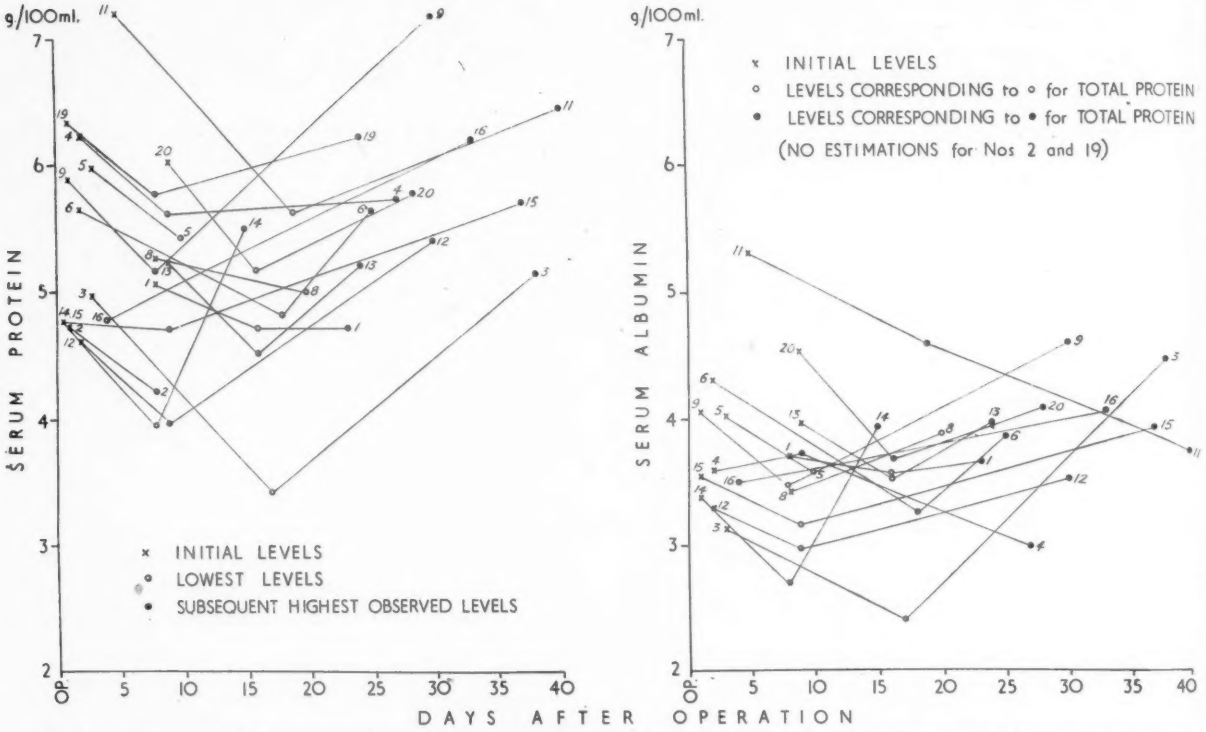

FIG. 6.—Changes in serum protein levels of sixteen infants in Group 1 during convalescence following operation for pyloric stenosis (steady progress).

Haemoglobin levels. Fig. 7 shows the haemoglobin levels of the four groups of infants compared with the average normal levels of artificially fed infants of similar ages, that is, one to five months (Horan, 1949). Since the normal haemoglobin curve is falling steeply during this period, the levels have been graphed as percentages above or below the standard levels. In this way they are shown in relation to the course of treatment. The levels of the premature infants are distinguished by (P) and those of the infants who received transfusions by (T). None of the levels estimated subsequent to transfusion has been recorded. The levels of the infants who made steady progress, Groups 1 and 3, have been separated from those in Groups 2 and 4 whose course was retarded by infection in sections (a) and (b) of Fig. 7. It may be seen that throughout the period of observation a larger number of the levels were below than were above the average for normal full term infants. The tendency to anaemia is slight, however, and if a lower curve (Mackay, 1933) had been used as the standard, it would not have been apparent. This finding is in accord with the results for the serum protein levels. Only three cases of severe anaemia (haemoglobin below 60 per cent.) occurred in the whole series of infants, and infection was present in two of them. These patients were among those who received transfusions. A higher incidence of anaemia might have been expected from descriptions in the literature of marasmic infants and, again, the food which our patients were receiving may explain the results.

Non-protein Nitrogen Levels

The non-protein nitrogen levels were estimated regularly on the same samples of blood as were used for serum protein and haemoglobin levels. The results show that the levels usually varied between 20 and 50 mg./100 ml. but occasionally high levels of the order of 80-90 mg./100 ml. were obtained. None of these was associated with a low serum bicarbonate level which would have indicated acidosis due to renal insufficiency. They were judged to be due to a high urea production from metabolism of the protein in the diet since the blood urea levels were also high. The levels tended to fall, and usually lay within the normal range if the intake of total calories was increased by the addition of carbohydrate.

Discussion

The process of recovery in wasted infants has not to our knowledge been studied fully, nor have reports of the progress of series similar to the present one been found in the literature. The early post-operative progress of infants with pyloric stenosis has been studied in relation to diet (Levi, methods for controlling infection as well as to better nutrition during the period of recovery.

No claim is made that the patients whose progress has been described were receiving optimum diets for their requirements. It is possible that other sources of protein besides casein might be used with advantage either in their natural or partially digested

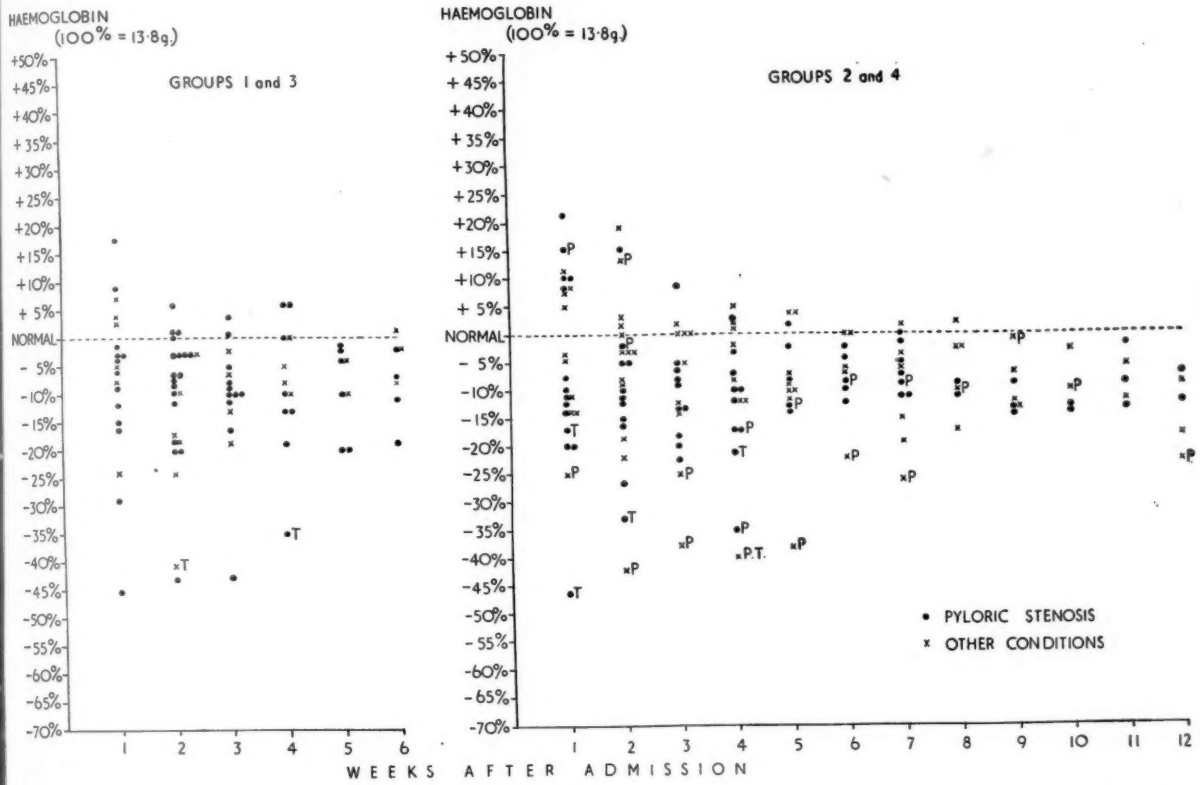

FIG. 7.—Haemoglobin levels of marasmic infants (a, Groups 1 and 3; b, Groups 2 and 4) compared with average levels for normal artificially fed infants (Horan, 1949). Each estimation has been expressed as a percentage above or below the average level for age.

1941), but the course of those suffering from marasmus was not separated from that of the babies whose obstruction was relieved before wasting became a prominent symptom. It has been asserted that gain in weight is often delayed for a considerable time in severely wasted infants (Utheim, 1920; Parsons, 1924). Most of the infants in the present investigation started to gain weight during the first week of treatment, and progress, even in those with definite signs of infection, was usually well maintained. Serious or chronic infection, however, was associated with an unsatisfactory course, as in case No. 4 (Group 4) who was suffering from multiple osteomyelitis. The free use of sulphadiazine and penicillin has undoubtedly contributed much to the good results which have been obtained. The relatively low incidence of hypoproteinaemia and of severe anaemia may also be due partly to these state. It has been shown, for example, that protein regeneration and haemoglobin production are stimulated by the administration of plasma, meat, and liver especially (Pommerenke, Slavin, Kariher and Whipple, 1935). The effects of these substances may be due to their amino-acid composition or to other less specific factors.

Many of the patients were discharged from hospital while they were still suffering from a severe degree of undernutrition, and our attention has been drawn to the need for a long period of after-care for such infants in order that they may reach a state of normal nutrition as soon as possible. The 4-5 oz. gain per week which is commonly accepted as adequate is insufficient to enable them to attain the normal weight range for their age and often a better rate can be achieved by improving the diet. Care should be taken also to protect marasmic infants

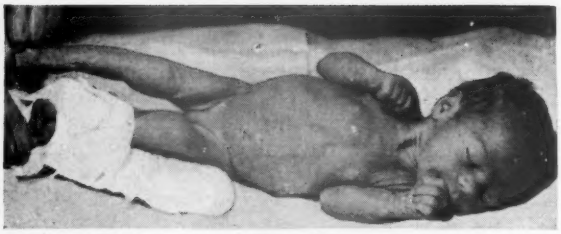

FIG. 8a.

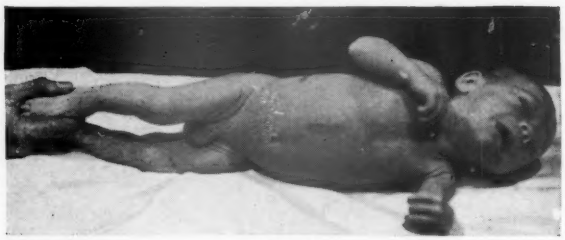

FIG. 8b.

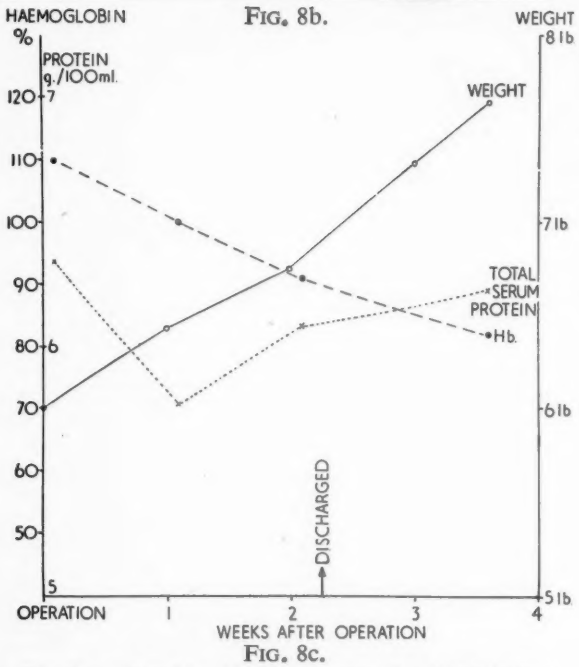

FIG. 8c.

FIG. 8a.—Case No. 19 R.H. (Group 1). Male infant aged four weeks, birth weight 7 lb. 3 oz. History of vomiting for ten days. Weight at operation 6 lb., i.e. 71 per cent. of expected weight. Post-operation feeding for marasmic infants with pyloric stenosis (table 2) followed closely. Patient discharged sixteen days after operation weighing 6 lb. 12½ oz. He was receiving 21 oz. per day of stage III feed (table 1) supplying 420 calories and 21 g. protein. At return visit eight days later weighed 7 lb. 10½ oz. and was receiving 24 oz. per day supplying 480 calories and 24 g. protein. The first photograph (fig. 8a) was taken before, and the second (fig. 8b) twenty-four days after operation. Fig. 8c shows weight gain, and serum protein and haemoglobin levels during same period.

from contact with infection; they are not only extremely susceptible but withstand it very badly. This may be partly due to a poor immunological response such as is known to be associated with protein depletion in animals (Cannon, Chase, and Wissler, 1943; Wissler, Wooldridge, Steffee Jr., and Cannon, 1946).

Studies of the metabolism of sick and wasted infants should be planned in order to obtain greater understanding of their requirements, particularly of nitrogenous foods. Further knowledge of their needs could now be readily applied, since digests of protein from various sources are available and could be given at an early stage of convalescence with little risk of intolerance by the alimentary tract.

Summary

Observations have been made on seventy-nine infants suffering from marasmus who weighed 80 per cent. or less of the expected weight before treatment.

The cause of the wasting was diagnosed and treated and efforts were made to improve nutrition without delay. Hydrolysed casein was used to augment the protein intake in the early stages of graded feeding, and later undiluted cows' milk mixtures were substituted. The feeds were arranged to provide about 120 calories and 6 g. of protein/kg./day throughout treatment.

Progress was assessed by the rate of gain in weight and recovery appeared to be made earlier and to proceed more regularly than before. If infection was present it sometimes did and sometimes did not retard the rate of recovery.

The serum protein and haemoglobin levels were estimated at weekly intervals for the periods during which the patients remained under hospital care. The changes in the serum protein levels were irregular but were sometimes found to be similar to those which have been described for animals and for adult man during periods of recovery from starvation and protein depletion. Severe hypoproteinaemia and anaemia were seldom found.

Many weeks may elapse before a wasted infant attains a good nutritional status. During this time special care is needed to ensure that he receives an optimum diet until his weight reaches the normal range for his age, and to prevent exposure to infection.

The authors wish to thank Professor Sir Leonard G. Parsons and Professor J. M. Smellie for their helpful criticism and advice, and the medical staff of the Children's Hospital, Birmingham, for allowing them to work in their wards. W.F.Y. received a grant from the Medical Research Council; E.A.B. and W.F.Y. each held the Caroline Harrold Research Fellowship, and Y.J.W. a research

scholarship from the Department of Paedriatrics and Institute of Child Health, of Birmingham University, during part of the time that these investigations were in progress. These awards are gratefully acknowledged.

The co-operation of the ward sisters has been invaluable in enabling this work to be carried out, and Mr. J. G. Williamson, the hospital photographer, has been of great assistance in preparing the diagrams.

The hydrolysed casein used in the investigation was supplied in part by the Medical Research Council and in part by the manufacturers.

References

Andersen, D. H. (1942). *Amer. J. Dis. Child.*, **63**, 643.
Cannon, P. R., Chase, W. E., and Wissler, R. W. (1943). *J. Immunol.*, **47**, 133.
——, Humphrey, E. M., Wissler, R. W., and Frazier, L. E. (1944). *J. Clin. Invest.*, **23**, 601.
Chow, B. F. (1946). *Ann. New York Acad. Sci.*, **47**, 297.
Cuthbertson, D. P. (1944). *Brit. Med. Bull.*, **2**, 207.
Davidson, L. S. P., and Fullerton, H. W. (1938). *Edinb. med. J.*, **45**, 1.
Fleming, G. B. (1921). *Quart. med. J.*, **14**, 171.
Himsworth, H. P. (1946). *Proc. Roy. Soc. Med.*, **40**, 27.
Horan, M. (1949). Personal Communication.
Jackson, R. L., and Kelly, H. G. (1945). *J. Pediat.*, **27**, 215.
Levi, D. (1941). *Brit. med. J.*, **1**, 963.
Mackay, H. M. M. (1933). *Arch. Dis. Childh.*, **8**, 221.
Marriott, W. McK. (1920). *Amer. J. Dis. Child.*, **20**, 461.
——, and Davidson, L. T. (1923). *Amer. J. Dis. Child.*, **26**, 542.
Mollison, P. L. (1946). *Brit. med. J.*, **1**, 4.
Parsons, L. G. (1924). *Lancet*, **1**, 687, 793, 939.
Pommerenke, W. T., Slavin, H. B., Kariher, D. N., and Whipple, G. H. (1935). *J. exp. Med.*, **61**, 261.
Poyner-Wall, P., and Finch, E. (1949). To be published.
Rossiter, R. J. (1946). *Nature*, **158**, 304.
Sabine, D. B., and Schmidt, H. R. (1943). *J. Lab. clin. Med.*, **28**, 1117.
Talbot, F. B. (1921). *Amer. J. Dis. Child.*, **22**, 358.
Utheim, K. (1921). *Amer. J. Dis. Child.*, **22**, 329.
Vaughan, J. (1948). *Brit. med. J.*, **1**, 35.
Walters, J. H., Rossiter, R. J., and Lehmann, H. (1947). *Lancet*, **1**, 205.
Weech, A. A., Goettsch, E., and Reeves, E. B. (1935). *J. Exp. Med.*, **61**, 299.
——, Wollstein, M., and Goettsch, E. (1937). *J. Clin. Invest.*, **16**, 719.
Wissler, R. W., Woolridge, R. L., Steffee, C. H. Jr., and Cannon, P. R. (1946). *J. Immunol.*, **52**, 267.

Correction:—Messrs. Wm. R. Warner, London, point out that 'beminal' which was referred to on p. 169 of the September issue is not marketed by their American company, Warner Bros., U.S.A., but by Ayerst, McKenna and Harrison of Montreal.

THE DIAGNOSTIC VALUE OF CARDIAC CATHETERIZATION IN ISOLATED PULMONARY STENOSIS AND LARGE INTERVENTRICULAR SEPTAL DEFECTS

BY

E. MANNHEIMER, M.D.
(From the Crown Princess Louisa Children's Hospital, Stockholm, Sweden)

Heart catheterization is a valuable aid in the diagnosis of congenital cardiac malformations of different types. This has been well known since the method was first adopted for clinical use by A. Cournand and his team (Cournand and Ranges, 1941). Bing in Baltimore and Dexter in Boston have both contributed excellent papers on the subject (Bing et al., 1947; Dexter et al., 1947). The monograph 'Cardiac Catheterization in Congenital Heart Disease' by Cournand, Baldwin, and Himmelstein (1949) gives us the results of cardiac catheterization in seventeen cases of congenital malformations of the acyanotic type. Nevertheless blue babies have been so much discussed during recent years that it may be of interest to add something about our experience and methods of catheterization in congenital heart disease without cyanosis.

We carry out catheterization as team work. In the beginning we worked with Lagerlöf and Werkö at St. Eric's Hospital, but since we were able to set up our own unit our team has consisted of Larsson, Möller, Landtman, and myself. Catheters of the Cournand type Nos. 6-9 and an intravenous drip infusion with 50 mg. of heparin in 1 litre of saline are used. Except in infants and in two or three older children we have not had recourse to general anaesthesia. We believe that in nearly all children

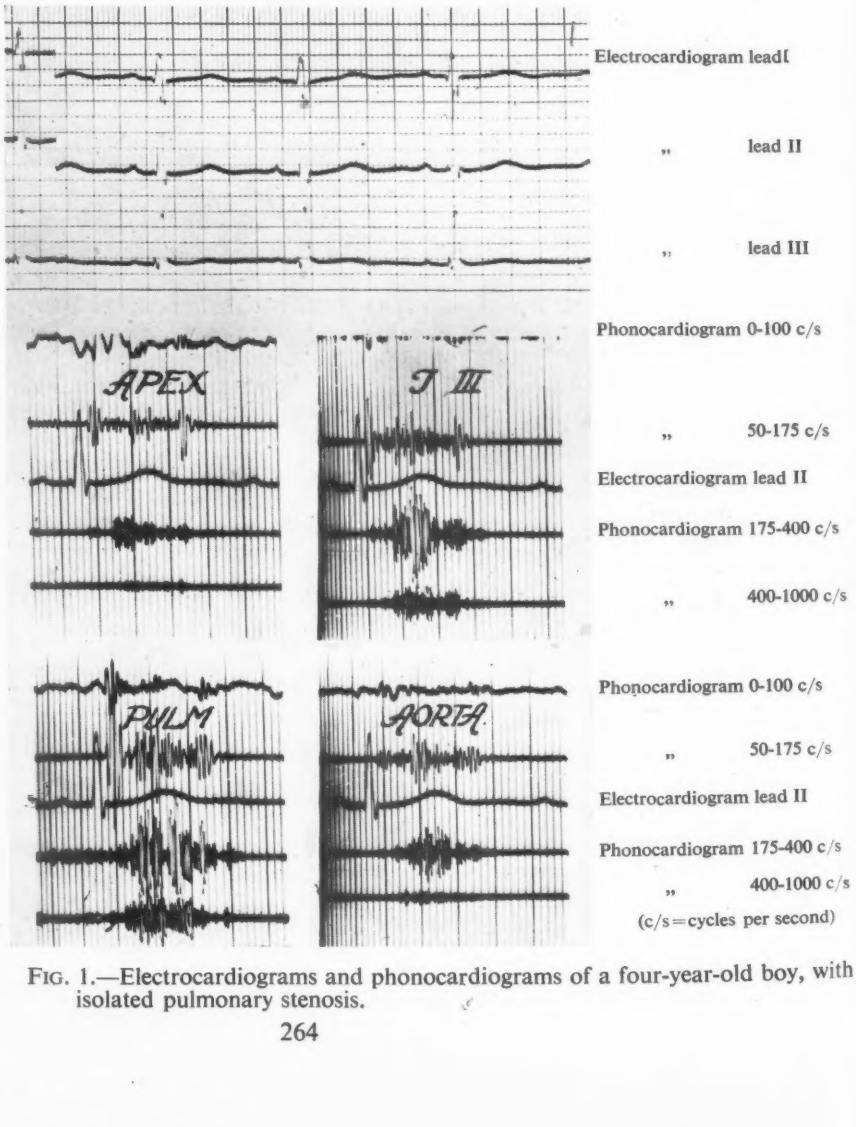

FIG. 1.—Electrocardiograms and phonocardiograms of a four-year-old boy, with isolated pulmonary stenosis.

there is less disturbance without anaesthesia provided the patients are handled in the right way. Blood samples are collected from as many places as the capacity of our laboratory will permit. The Tybjaerg-Hansen pressure apparatus containing a condensator-manometer and an amplifier is used in all cases. It is of great value to have good pressure equipment, and we consider that a water manometer which gives mean values only is not sufficient. Our recording apparatus consists of an Elmquist electrocardiograph permitting the simultaneous recording of six tracings, and an apparatus for calibrated phonocardiography (Mannheimer-Stordal type). The oxygen consumption is determined by means of Douglas bags and the gas is analysed in a Haldane apparatus. We use arterial puncture (most often of the femoral artery) in nearly every case in order to obtain values for the arterial oxygen content, arterial oxygen saturation, and oxygen capacity of the blood. By means of these values and the Fick method approximate figures are calculated for the pulmonary and systemic flows and for shunts.

In order to limit myself to those groups of congenital cardiac malformations in which cardiac catheterization has shown new aspects, I have chosen two types, (1) isolated congenital pulmonary stenosis without over-riding aorta, and (2) large interventricular septal defects. Both these groups have some signs in common. First, a loud, harsh systolic murmur immediately leads to the diagnosis of congenital heart disease. Secondly, a more or less pronounced bulging of the pulmonary arc is present in both. In the third place, hypertension in the lesser circulation is a characteristic sign, even if it is not present in all cases.

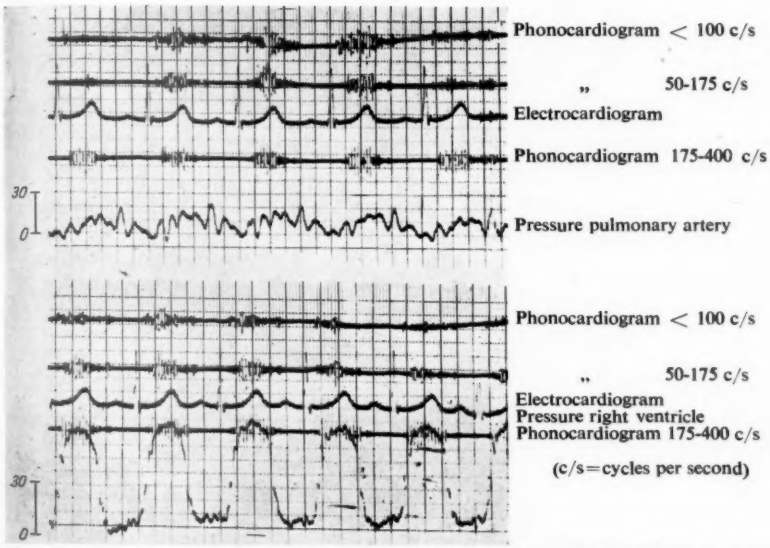

FIG. 2.—Pressure tracings obtained during cardiac catheterization in a case of isolated pulmonary stenosis.

Pulmonary Stenosis

The St. Eric's team and ours have seen seven cases of isolated pulmonary stenosis during the last two years. These seven cases differ from the earlier conception of this disease. No cyanosis is present, and the symptoms are so mild that affected persons can live quite a normal life; there is no retardation in growth and only slight limitation of activity. Physical examination reveals a loud, harsh systolic murmur over the pulmonary orifice (fig. 1) and x-ray examination shows a moderately bulging pulmonary arc. The arterial oxygen saturation is normal (96 per cent. to 98 per cent.) and does not drop more than 4 per cent. to 5 per cent. during exercise, which is normal. In testing arterial oxygen oximeter recordings are helpful, as they make most of the van Slyke determinations superfluous.

It is obvious that in most of the cases the pressure in the right ventricle is pathologically increased (normal value 30 mm. Hg), and in some of the cases to a very high degree. In our opinion this increase in right ventricular pressure above the arterial blood pressure must indicate that no over-riding aorta is present. The highest pressure in the right ventricle was 170/0 and the lowest 58/9. The pressure in the pulmonary artery is always lower than that in the right ventricle, and this fact establishes the diagnosis of a pulmonary stenosis. Withdrawal tracings prove that this stenosis is an infundibular one.

Fig. 2 gives pressure tracings from a boy with isolated pulmonary stenosis.

The blood gas analyses give on the whole no significant differences in oxygen contents. In all cases there is a slightly higher oxygen content in the pulmonary artery than in the right ventricle. A patent ductus arteriosus seems, however, rather unlikely as no continuous murmur is present. One case, a 25-year-old woman, was operated on by Crafoord many years ago. The exploratory thoracotomy showed a wide pulmonary artery but no patent ductus arteriosus. The high oxygen content in the pulmonary artery could be due to a small high interventricular septal defect or more probably to random variation.

All seven cases show more or less pronounced post-stenotic dilatation of the pulmonary artery. It is this dilatation that causes the bulging pulmonary arc and also gives rise to the suspicion that these are cases of patent ductus arteriosus. Previously we used to speak of idiopathic pulmonary dilatation. There is no doubt that many of the cases belonging to this group will prove to be cases

of isolated pulmonary stenosis with post-stenotic dilatation.

Interventricular Septal Defects

The new aspects of interventricular septal defects revealed by cardiac catheterization are shown in fig. 3. In all cases the clinical diagnosis was interauricular septal defect, or perhaps a Lutembacher syndrome (atrial septal defect and mitral stenosis), because these signs were observed: retardation in growth; acyanotic, pale, tiny children; harsh systolic murmur; enlarged heart with marked bulging of the pulmonary arc; and a very pronounced increase in the pulmonary flow showing marked pulsations of the pulmonary artery and hilar dance. In all cases the right auricle was moderately enlarged. After cardiac catheterization was carried out one of these cases (P.E.L.) proved to be a patent ductus with a difference in oxygen content between the pulmonary artery and right ventricle of nearly 4 vol. per cent., thus indicating a left to right extracardial shunt through the ductus of about 80 per cent.

The second case (R.A.) was that of a 10-year-old girl. She was a thin, under-developed child and was classed among the morbus coeruleus cases because of slight cyanosis after exercise. X-ray examination showed a picture which suggested an auricular septal defect or a Lutembacher syndrome. The very slight cyanosis and the marked physical under-development pointed the same way. Catheterization, however, revealed a huge ventricular septal defect, with an enormous left to right shunt of about 80 per cent. Thus this heart functioned as a cor triloculare with a common ventricle, the oxygen content of the right ventricle and that of the femoral artery being almost equal. Because of the large left to right shunt, pressure in the right ventricle and pulmonary artery as well as the pulmonary flow were markedly increased. It was of interest that the murmur had its maximal intensity over the pulmonary orifice, although the septal defect was of ventricular origin. The case shows how difficult or even impossible it is to make the correct diagnosis in vivo without catheterization of cases with systolic murmurs and thrills along the left sternal border when there is little or no cyanosis.

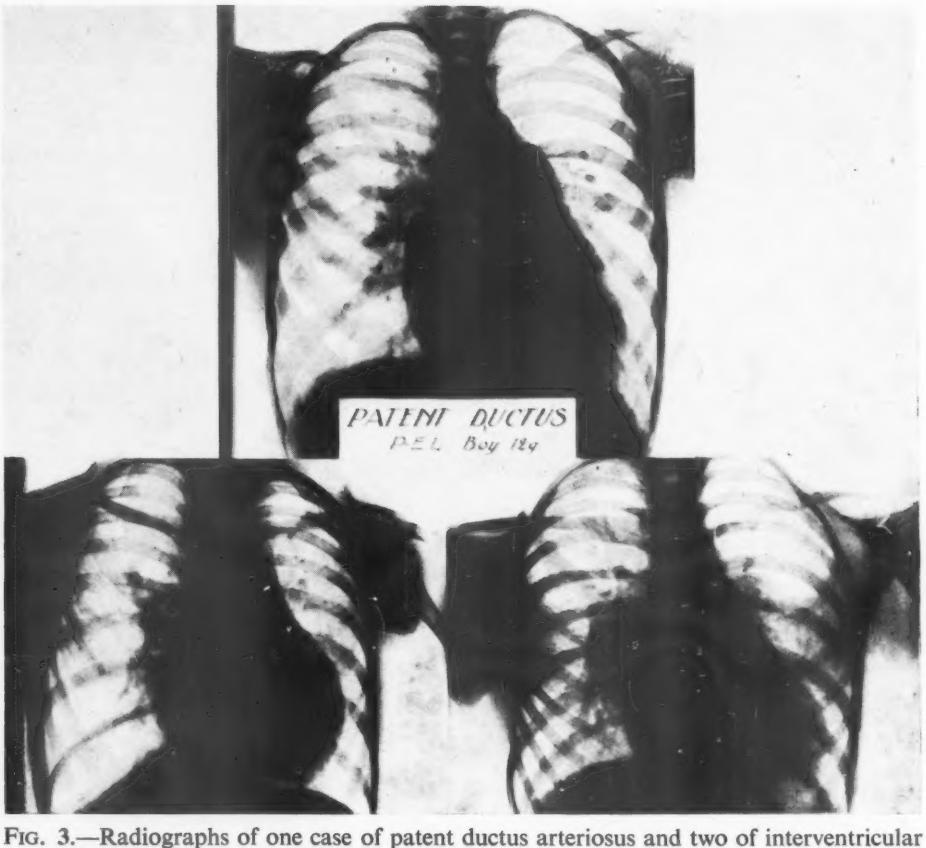

FIG. 3.—Radiographs of one case of patent ductus arteriosus and two of interventricular septal defects; all three showed evidence of increased pulmonary blood flow.

Fig. 4 gives the results of cardiac catheterization in this case. Calculating the flows and the shunt

from the differences in oxygen content, the pulmonary flow is five times as large as the systemic flow. In other words, of the amount of blood coming from the lungs and reaching the left heart, 80 per cent. is shunted into the right ventricle and out into the pulmonary artery again. The pressure in the right ventricle and the pulmonary artery is markedly increased and probably about the same as the left ventricle. During systole both ventricles communicate and consequently the systolic pressure will be the same.

In this connexion the third case (B.K.) may be worth mentioning. The clinical picture was the same; the shunt was also very large (75 per cent.) but the pressure in the lesser circulation was normal (Fig. 5). This suggests that the interventricular septal defect did not function during systole. Otherwise the pressures in both ventricles would instantly have been balanced. It is possible that the defect either closed during the systole, perhaps by muscular contraction, or remained anatomically open but no shunt took place (Eek, personal communication).

Summary

Isolated pulmonary stenosis is not a very rare type of congenital heart disease. Patients with this anomaly can live a normal life and the prognosis seems to be remarkably good. The diagnosis is made entirely by cardiac catheterization. Idiopathic pulmonary dilatation as previously described may actually be isolated pulmonary stenosis with poststenotic dilatation.

Patent ductus arteriosus with enlarged heart and a large shunt, interauricular septal defects, and large interventricular septal defects often cannot be differentiated clinically. Cardiac catheterization gives the diagnosis in these cases. In many cases with septal defects between the ventricles there is equal pressure in both ventricles. In these the septal defect is undoubtedly open during the systoles. In some other cases, also with large interventricular shunts, the pressure in the right ventricle is normal and much lower than that in the left ventricle. In these cases it is suggested that the defect is anatomically or functionally closed during the systole.

This study would seem to indicate that the classical textbook description of interauricular septal defect is not

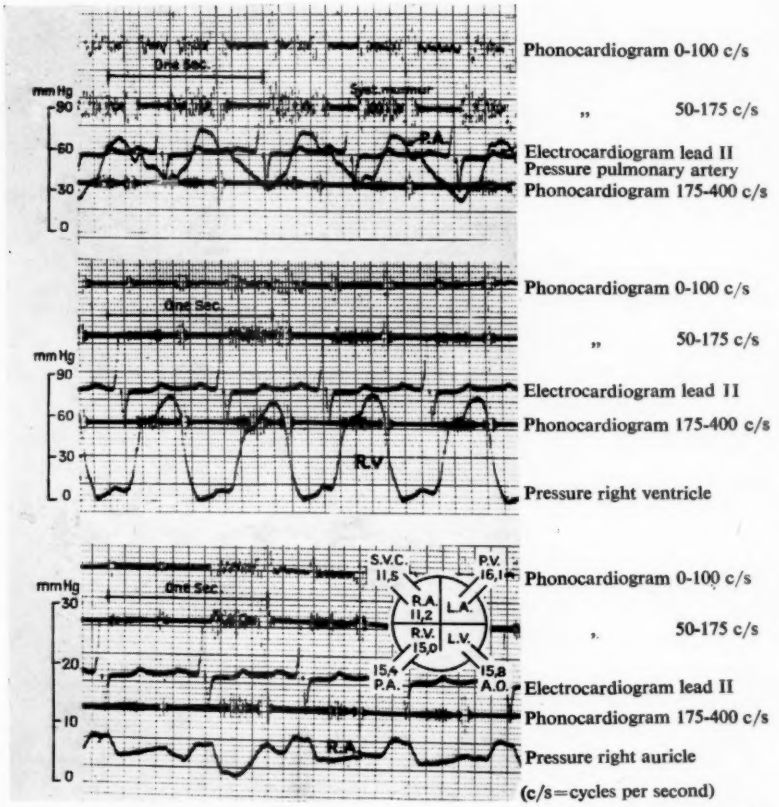

FIG. 4.—Pressure tracing obtained during cardiac catheterization in a case of ventricular septal defect.

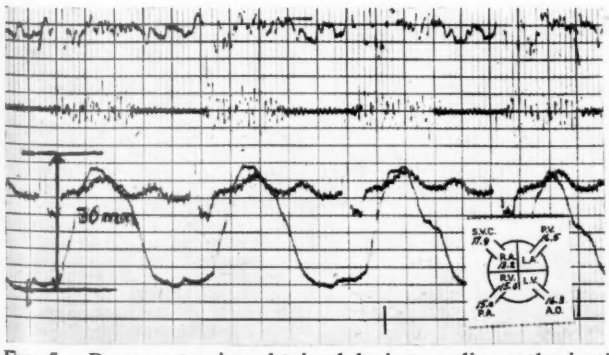

FIG. 5.—Pressure tracing obtained during cardiac catherization in a case of ventricular septal defect in which probably there was no shunt during the systole.

entirely satisfactory. Such a diagnosis should not be made clinically without a thorough examination, including cardiac catheterization.

References

Bing, R. J., Vandam, L. D., and Gray, F. D., Jr. (1947). *Bull. Johns Hopk. Hosp.*, **80**, 107, 121, 323.

Cournand, A., and Ranges, H. A. (1941). *Proc. Soc. exp. Biol.*, **46**, 462.

Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C., and Evans, J. M. (1947). *J. clin. Invest.*, **26**, 615.

Handelsman, J. C., Bing, R. J., Campbell, J. A., and Griswold, H. E. (1948). *Bull. Johns Hopkins Hosp.*, **82**, 615.

Hansen, A. T. (1947). *International Physiolog. Congress, Oxford.*

Mannheimer, E., Larsson, Y., Lagerlöf, H., Möller, T., and Werkö, L. (1949). *Acta Paediatr.*, to be published.

SYMMETRICAL CORTICAL NECROSIS OF THE KIDNEYS IN INFANCY AND CHILDHOOD

A. COLIN P. CAMPBELL, M.B., F.R.C.P.E., and
J. L. HENDERSON, M.D., F.R.C.P.E.

(From the Departments of Pathology and Child Life and Health, University of Edinburgh)

Symmetrical cortical necrosis of the kidneys is very uncommon. Apparently the first authentic description of the condition was given by Juhel-Rénoy in Paris in 1883, the patient being a young woman aged sixteen years. Since that time about one hundred cases have been published, most of them in the last twenty years. The disease is best known as a complication of pregnancy, but it may occur in non-pregnant women, males, and children; about two-thirds of the reported cases have been associated with pregnancy and many of the remainder with bacterial infection. Duff and More, who reviewed the literature up to 1941, analysed seventy-one cases, forty-eight associated and twenty-three not associated with pregnancy; but Dunn and Montgomery, in the same year, published fifteen cases of which only seven were associated with pregnancy. The age distribution of cases not associated with pregnancy has been widely scattered through childhood, adolescence, and maturity, and there has not been any significant difference in the sex incidence in this group.

Records of only nine cases of bilateral cortical necrosis of the kidneys occurring in children under fifteen years of age have been found in the literature. The apparent rarity of the disease in childhood has induced us to review these cases and to record four more. Two of our cases occurred in infants, the patients being aged 9 weeks and 24½ weeks respectively. These are of particular interest since the disease has never before, to our knowledge, been reported in infancy. The fact that three of our cases were observed within a period of nine months, in a community of barely half a million inhabitants, shows that the disease is not as rare in infancy and childhood as the paucity of reports in the literature suggests.

Case Records

Case 1. E.D., a girl aged 10½ years, was admitted to the Children's Unit, Western General Hospital, Edinburgh, on Oct. 20, 1947, with a history of recurrent abdominal pain for two years. At first the pain had been felt at intervals of two to three weeks, but it became more frequent and latterly occurred at intervals of a few days. The attacks tended to be concentrated in groups and 'to be accompanied by fever.' The intensity of the pain became worse and latterly was very severe. It was centrally placed, had an aching character, and usually lasted a few hours. It developed at any time, but eating sometimes precipitated it, causing the child to be afraid to eat her meals. Vomiting had accompanied the pain on one occasion only. Loud borborygmi had been very troublesome in recent months. According to the mother there had not been any constipation or diarrhoea. The child had been losing weight in recent months and 'no longer plays and dances.' Her progress at school had become less satisfactory. The patient was a small, slender girl of poor nutrition who weighed only 48 lb. Skin tone was fair and muscle tone poor. The mucous membranes were healthy. She looked tired.

ALIMENTARY SYSTEM. The mouth was healthy, the tongue clean and moist. The child indicated that the pain, when present, was periumbilical, and she complained of slight, indefinite tenderness in that region on palpation, but there was no muscular guarding and nothing abnormal was palpated in the abdomen. Digital examination of the rectum was also negative. Radiological examination of the alimentary tract with a barium series revealed some dilatation of the lower ileum, also some narrowing and irregularity in the ileo-caecal region suggestive of ileo-caecal tuberculosis.

RESPIRATORY SYSTEM. Physical examination was negative. Radiological examination of the chest showed a few calcified glands at the left hilum, but the chest was otherwise normal.

CARDIOVASCULAR SYSTEM. A soft systolic murmur was heard in the mitral area.

HAEMOPOIETIC SYSTEM. No enlarged lymphatic glands could be palpated, and the spleen was not enlarged.

Blood examination gave the following results:

Haemoglobin, 80 per cent. (Sahli).
Erythrocytes, 5·02 million per c.mm.
Leucocytes, 7,000 per c.mm.
Differential count, normal.
Blood sedimentation rate (Westergren), 23 mm. in one hour.

There was no abnormality in the urine.
A Mantoux test (1 in 1,000) was positive.

During the first six days in hospital there was no abdominal pain, but constipation was troublesome, the bowels acting on alternate days and aperients being necessary.

On the seventh day severe lower abdominal pain with maximal intensity in the right iliac fossa suddenly developed. The constipation had been corrected before the onset of this pain and a normal motion was passed a few hours before it began. There was no vomiting. Digital examination of the rectum was negative. The temperature was not elevated. Leucocytes numbered 10,000 per c.mm.

The child was examined three hours after the onset of the pain by Mr. Mason Brown, paediatric surgeon, who immediately performed a laparotomy. Nitrous oxide and ether anaesthesia was used. A considerable amount of turbid free fluid was found in the peritoneal cavity and the mesenteric glands were enlarged and inflamed. The peritoneal exudate contained large numbers of polymorphs, scanty fibrin, serosal cells, and clumps of cocci, but there were no tubercle bacilli. The appendix looked normal and was removed: histologically it showed no abnormality, nor was there any evidence of tuberculosis. The wall of the terminal part of the ileum was congested and thickened and there was a partial obstruction near the proximal end of the abnormal segment of bowel. The omentum adhered to a grey, fibrinous patch on the wall of the ileum in the latter situation. The wall of the caecum was contracted and thickened and was bound to the posterior abdominal wall by adhesions. A diagnosis of ileo-caecal tuberculosis was made, and the obstruction towards the lower end of the ileum was short-circuited by an ileal anastomosis. Convalescence was satisfactory for thirteen days during which there was no further abdominal pain or constipation.

On the first day of the terminal illness nausea, vomiting, and diarrhoea developed fairly suddenly and the child looked pale and ill within a few hours. The stools contained mucus and were streaked with a little blood. Bacteriological examination of the stools did not reveal any organisms of the enteric or dysentery groups, and no tubercle bacilli were found in a direct film or on culture; the two guinea pigs inoculated died of intercurrent disease. The vomiting remained persistent and severe on the first day of the symptoms and there were four diarrhoeal stools. There was no fever. A provisional diagnosis of gastro-enteritis, possibly Sonne dysentery, was made and the patient was isolated. Small amounts of glucose water and dilute milk were given at frequent intervals, and a course of sulphamezathine (1 g. four-hourly) was begun.

Persistent vomiting continued during the second day, but there was only one stool (a.m.). The child looked very pale and ill. The leucocyte count had risen to 16,000, the haemoglobin had fallen to 70 per cent., and the erythrocytes to 4·2 million. It was noticed that she did not void any urine after the morning of this day.

Vomiting persisted on the third day and the general condition had become worse. There was no further bowel movement. Complete anuria persisted. Catheterization of the bladder produced only a few ml. of urine which contained a large amount of albumin, and, on microscopical examination, only a small number of erythrocytes. The temperature remained normal. The blood pressure was 115 mm. Hg systolic and 70 mm. Hg diastolic. Sulphamezathine was discontinued in the afternoon of this day after a total amount of 12 g. had been administered in the previous forty-eight hours, of which a considerable, but unknown amount, had been ejected in the vomitus. On this day the child received 14 oz. of fluid orally and 1 pint of 5 per cent. glucose in normal saline intravenously.

On the fourth day complete anuria persisted and there was no further stool. Vomiting persisted. The blood pressure was slightly elevated, being 120 mm. Hg systolic and 70 mm. Hg diastolic. There was a generalized convulsion at 1.45 p.m. after which she remained unconscious and very restless with some spasticity of the limbs and athetoid movements of the hands. Lumbar puncture yielded clear cerebrospinal fluid under normal pressure. The only abnormality in the fluid was a slight increase of protein to 50 mg. per cent. The blood urea nitrogen had attained a high level on this day, being 130 mg. per cent. Six hours after the onset of unconsciousness the coma became deeper and the restlessness diminished. The blood pressure remained at its former level. The pulse rose in the evening to 140 per minute. There were no focal signs of nervous disease on examination of the superficial and deep reflexes and ocular fundi. On this day the child received one pint of 5 per cent. glucose in half-normal saline intravenously. Sodium sulphate, 200 ml. of a 4·8 per cent. solution, was then given intravenously followed by 50 ml. of a 50 per cent. glucose solution six hours later. To diminish the restlessness and muscular hypertonia, sodium phenobarbitone, 1½ gr., was given intramuscularly.

The child's condition continued to deteriorate on the fifth day with persistent anuria and coma. The pulse rate still rose, and the temperature for the first time reached 100° F. There was one motion eight hours before death after a lapse of three days. The child died in the forenoon of this day, twenty hours after the beginning of coma. After the onset of unconsciousness 1½ pints of 5 per cent. glucose in a quarter normal saline had been given intravenously in addition to the sodium sulphate and hypertonic glucose.

NECROPSY (performed five hours after death). The body was that of a girl of slight build, rather poorly nourished. The abdomen showed a recent operation incision, healing satisfactorily.

The pleural sacs each contained about 100 ml. and the pericardial sac about 80 ml. of clear yellow transudate. The peritoneal sac contained only a few ml. of similar fluid.

The upper lobe of the left lung and hilar lymph nodes showed an apparently quiescent primary tuberculous complex, with caseation, fibrosis, and calcification.

The peritoneal cavity showed fibrinous adhesions as the result of the recent operation, and in addition occasional old fibrous adhesions between loops of bowel and around the spleen; very occasional isolated small grey tubercles were present in the peritoneum of the small and large intestine. Four strictures with shallow transverse healing ulcers were found, three in the small intestine and one in the transverse colon. There was no appreciable distension of any part of the bowel. The uppermost of these stenosing ulcers, at the lower end of the jejunum, had been short-circuited by a recent, healthily healing, side-to-side anastomosis. The appendix had recently been removed. The lower three feet of the ileum showed uniform intense congestion and swelling of the mucosa, with semi-confluent haemorrhages, and a fibrinous exudate on the peritoneum. The mesenteric lymph nodes were considerably swollen, soft, and of a uniform dusky red appearance on section; they showed no sign of tuberculosis.

The kidneys were of identical appearance. They were slightly swollen, the subcapsular surface was smooth but considerably congested, and thickly studded with tiny haemorrhages. On section, cortex and medulla were both uniformly congested, and the cortex was studded with petechiae throughout. The consistence was slightly softened. The bladder was empty.

The liver showed cloudy swelling.

Brain and meninges, mouth, neck organs, heart, aorta, stomach and duodenum, bile passages, pancreas, suprarenals, spleen, uterus, ovaries, and bone marrow all appeared normal.

On histological examination both kidneys showed the same picture of severe cortical damage (fig. 1). The glomeruli were almost all affected, though in varying degree; there was great dilatation of the capillary loops, though not necessarily of all the loops of any individual tuft; most of the dilated loops contained uncoagulated red cells, but a large minority was plugged by eosinophil homogeneous or fibrillar material which gave the staining reactions of fibrin; sometimes these fibrin thrombi did not completely occlude the lumina, but formed crescentic or ring-like mural deposits. The most severely damaged glomeruli showed karyorrhectic necrosis of all the cells; those less damaged showed considerable swelling and proliferation of the epithelium covering the tuft, and slight swelling (but no proliferation) of the capsular epithelium. Both capsular and tuft epithelial cells showed colloid droplet degeneration. The capillary endothelium of the less severely damaged glomeruli showed a little swelling in some loops. In many glomeruli the capsular space contained free red cells.

Most of the cortical tubules showed patchily distributed coagulative necrosis. Areas where every tubule was necrotic alternated with areas where the necrosis was limited to the proximal convoluted tubules; the ascending limbs of Henle's loops, the distal convoluted tubules, and the collecting tubules were spared. The areas of severest tubular damage coincided with those where the glomerular changes were most marked. In the least damaged areas some of the proximal tubules had escaped necrosis. They showed various degenerative changes, however: cloudy swelling, a good deal of colloid droplet degeneration, and occasionally considerable dilatation. Some of the tubules contained red cells, others necrotic epithelial debris, polymorphs or hyaline material.

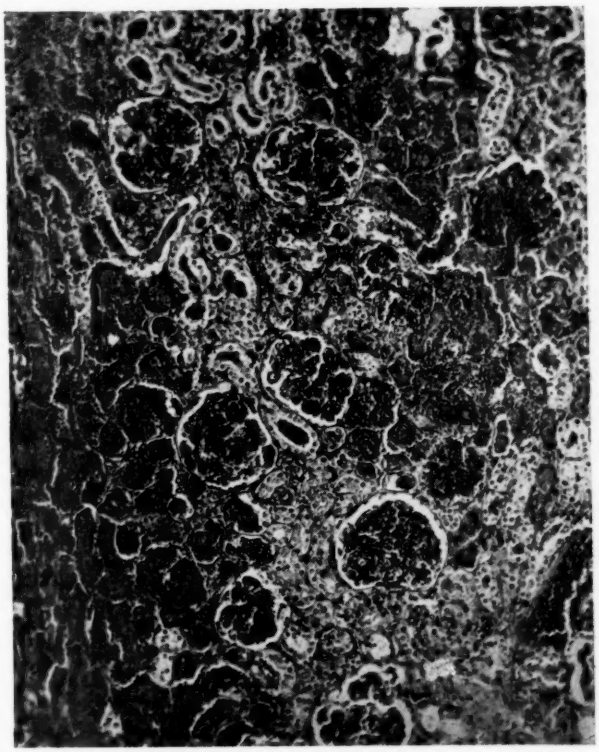

FIG. 1.—Photomicrograph of renal cortex (Case 1), showing characteristic great glomerular congestion and extensive patches of tubular necrosis (darkly stained areas). Haematoxylin and eosin. ×70.

These glomerular and tubular changes showed a tendency to zonal variation; a narrow subcapsular zone, and a wider zone in the juxtamedullary cortex were relatively sparse.

The tissue was nowhere completely necrotic; even where every tubule showed necrosis of its epithelium the interstitial cells survived. Nor was there any sign of thrombosis in the intertubular capillaries. The more severely damaged areas showed a good deal of polymorph infiltration of the interstitium as well as of the necrotic tubules.

The medulla showed little abnormality; the tubules contained casts (mainly hyaline, occasionally granular), but their epithelium appeared healthy.

Apart from the glomeruli the blood vessels showed little abnormality; fibrin thrombosis extended back from a few of the glomeruli into the terminal parts of their afferent arterioles, and a few other afferent arterioles, which were not thrombosed, showed red cells, and a little fibrin in their walls. Other afferent arterioles appeared slightly dilated but otherwise normal. The interlobular arteries showed slight dilatation, but no

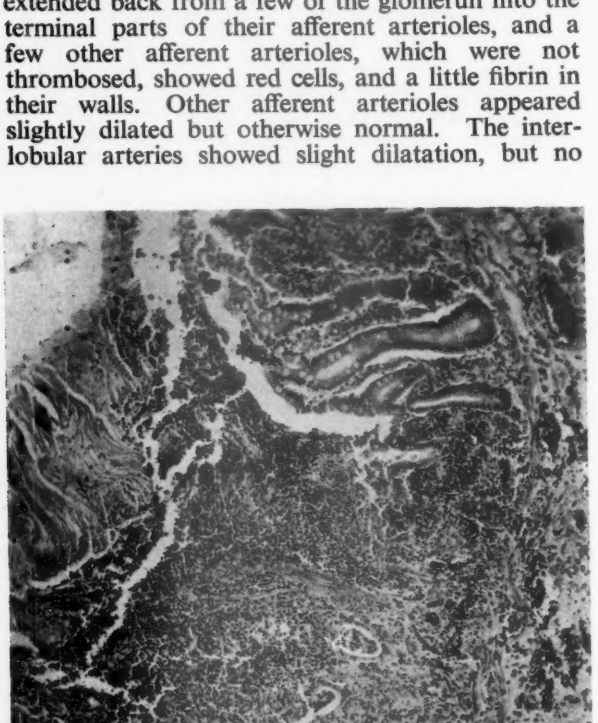

FIG. 2.—Photomicrograph of ileum (Case 1), showing patch of necrosis of mucosa, and oedema, congestion, and haemorrhage in the submucosa. Haematoxylin and eosin. ×70.

thrombosis, intramural haemorrhage or fibrin deposition. The arcuate arteries were normal. The interlobular veins were considerably dilated, but showed no other change. The cortical intertubular capillary bed was moderately congested and the vasa recta of the medulla were markedly so, but no thrombosis was seen in either.

Sections of the ileum from the area of haemorrhagic enteritis showed great congestion of mucosa and submucosa, but the muscular and subserous coats appeared normal. The submucosa was very oedematous; the mucosa showed semi-confluent haemorrhage, and many small patches of coagulative necrosis (fig. 2); there was on the surface a fibrin-polymorph exudate, adherent to, and apparently emanating from the necrotic patches; polymorph infiltration, however, was not generalized. Some of the necrotic patches showed little or none. There was no ulceration. The capillaries and venules of the submucosa were greatly congested, and some of the venules were plugged by thrombi of mixed fibrin-platelet type. The arterioles varied in calibre from contraction to moderate dilatation; many showed fibrinoid infiltration of the intima, but only rarely thrombosis.

A section from one of the stenoses showed healed ulceration; a depression of the mucosal surface, covered by regenerated mucosa, deep to which there was scar tissue formation replacing the inner muscle coat. There was no sign of active tuberculosis.

A mesenteric lymph node showed congestion and some polymorph infiltration. It contained an old encapsulated caseous area but there was no sign of active tuberculosis.

The lungs showed mild acute bronchitis.

The appendix (removed at operation), and the liver, spleen, pancreas, and suprarenals showed no significant abnormality.

Case 2. H.M., a girl, aged 4½ years, was admitted to a surgical ward, Royal Infirmary, Edinburgh, on Feb. 17, 1938, with a history of recurrent tonsillitis and cervical adenitis for one year. Tonsillectomy was performed twelve days before admission to hospital. The child seemed to recover well from the operation but the enlarged cervical glands on the left side became larger. Three days before admission she developed pain in the right hip. The pain was worse the following day and there was obvious fever. Pain, fever, and disturbed sleep continued until admission. There is no record of urinary symptoms.

On examination, development and nutrition were considered satisfactory. Movements at the right hip joint were restricted, and external and internal rotation were painful. There was tenderness on firm palpation over the head of the femur. No other abnormalities were recorded.

A radiograph of the right hip joint taken the day after admission showed:

> 'Joint space slightly widened with probable distension of the joint capsule and slightly increased density of the soft tissue shadows around the joint. The appearance is consistent with early acute arthritis.'

The temperature reached 103·8° F. on the day after admission, varied between 99·0° F. and 101·0° F. on the three following days, and thereafter never exceeded 99·4° F. Diarrhoea developed five days after admission and the child passed nine stools that day. Drowsiness and slight head retraction were also observed on the same day. Less severe diarrhoea persisted for the following two days. There is no record of melaena.

Dysentery was suspected but bacteriological examination of the stools did not reveal any pathogens.

The drowsiness and head retraction became worse. Internal strabismus developed four days after the beginning of these signs. Lumbar puncture was unsuccessful. A fatal epileptiform seizure occurred at 12.30 p.m. on the same day, nine days after admission and four days after the onset of diarrhoea.

There is no record of the frequency of micturition or of urine examination.

NECROPSY (performed forty-six hours after death). The body was that of a well developed, well nourished child.

The right hip joint contained thick pus, from which a haemolytic streptococcus was isolated.

The kidneys were of normal size, and of identical appearance. In each the subcapsular surface was congested and thickly studded with small haemorrhages. On section the cut surface showed great congestion, with many small haemorrhages throughout the cortex.

The large intestine showed a segmental lesion affecting the whole of the pelvic colon; the wall of this segment was greatly swollen by haemorrhagic oedema affecting the entire thickness; the serous surface showed a localized fibrinous peritonitis. The appearance suggested haemorrhagic infarction from inferior mesenteric artery thrombosis, but no such thrombosis was found.

The brain showed moderate congestion of the lepto-meninges, and very slight flattening of the cerebral gyri. A haemolytic streptococcus was isolated from the basal cerebrospinal fluid.

The spleen showed slight softening and congestion of the pulp, without obvious enlargement, and the liver and myocardium cloudy swelling. The other organs showed no significant abnormality.

On histological examination of the kidneys the following changes were seen throughout the several sections examined. Almost every glomerulus was affected, showing either great congestion or, in many cases, fibrin thrombosis of the capillary loops; some capillaries showed a tubular layer of fibrin with a still patent lumen. Some of the fibrin thrombi stained diffusely with Scharlach R. Occasional glomeruli were completely necrotic. Extravasated red cells were seen in the capsular spaces of a few glomeruli (occasionally accompanied by fibrin) and in a few convoluted tubules, both proximal and distal. The less severely damaged glomeruli showed slight swelling and a little fatty degeneration of the visceral epithelium. The subcapsular glomeruli were slightly, and the juxtamedullary glomeruli considerably, less severely affected. Tubular changes were confined to the proximal convoluted tubules; complete necrosis was seen only in occasional small groups; many others, however, showed nuclear pyknosis with necrosis and granular disintegration of individual cells. Many of the less affected tubules showed marked colloid droplet degeneration, others only cloudy swelling or post-mortem change.

The interstitium of the cortex showed a profuse, semi-diffuse polymorph infiltration, which was not confined to the neighbourhood of the foci of frank tubular necrosis. There were occasional interstitial haemorrhages.

The afferent arterioles were dilated. Many showed infiltration of red cells and sometimes fibrin into their walls. Some were occluded by fibrin thrombi. The interlobular arteries showed only slight dilatation. The arcuate arteries appeared normal.

The medulla showed marked congestion of the vasa recta, but was otherwise normal.

The entire wall of the pelvic colon was grossly oedematous and heavily infiltrated by red cells. Post-mortem change prevented further analysis.

The spleen showed a banal acute infective reaction.

The liver, lung, and myocardium showed no significant abnormality. Sections of the brain were not available.

Case 3. J.W., a girl, aged 5½ months at death, was admitted to the Gastro-enteritis Unit, City Fever Hospital, Edinburgh, on July 17, 1948, with a history of vomiting and diarrhoea for six days. The baby had been well until six days before admission when she began to sneeze and cough and to vomit after each feed. The same night the stools became loose and ' blackish-green with blood among them.' The milk feeds were stopped and glucose water given. The vomiting ceased at the end of the second day, but the stools remained loose and interspersed with a considerable amount of blood. Moreover she had ' bouts of crying as if in pain.' During the first three days of the illness she continued to feed fairly well, did not seem feverish, and looked only slightly ill. Pink staining of the napkin was noticed during this phase, but it was not possible to determine from the history whether this was caused by melaena, which was definitely present, or by haematuria, which may have been present, particularly in view of the later history, or by both.

After three days of illness the baby was taken to the Medical Out-Patient Department at the Royal Hospital for Sick Children, Edinburgh, where a diagnosis of acute gastro-enteritis was made. She did not look unduly ill. A loose yellow stool without visible blood was seen on the napkin but no pink urine staining was observed. She was treated at home for the next three days on a diluted milk mixture with sulphaguanidine, 0·5 g., four times a day. She then returned to the Medical Out-Patient Department where her general condition was found to have deteriorated, though she did not appear to be very ill. Vomiting had occurred after most feeds for the last two days. Diarrhoea had persisted with four or five loose green stools per day.

On admission to hospital the patient was seen to be a well developed, well nourished baby, weighing 14 lb. The skin and conjunctivae were pale. She looked alert and was not unduly fretful or dehydrated. The mouth was rather dry and the

tongue was slightly furred. The buttocks were excoriated on each side of the natal cleft.

During the first day in hospital the stools were frequent, dark brown, and watery, with mucus, and, sometimes, a trace of blood. No enteric or dysentery organisms were isolated from them. Vomiting was also frequent, the vomitus being clear fluid containing traces of coffee-ground material and a little mucus. During the remainder of this day Hartmann's solution was given by mouth and no drugs were given. By the second day the infant's general condition had deteriorated. She fed reluctantly and the pallor had increased. The diarrhoea and vomiting continued and the vomitus, which still contained coffee-ground material, had now become bile-stained. Alarm was felt at the child's failure to pass any appreciable quantity of urine since admission on the previous day, although a small pinkish stain on the napkin, thought to have been caused by urine, was seen on four occasions within the first twenty-four hours after admission. Catheterization was carried out several times but no urine was obtained. A slight degree of generalized oedema was noticed, particularly in the face.

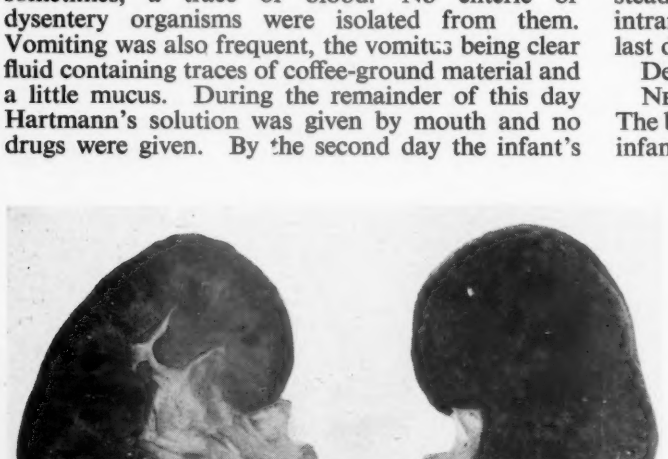

FIG. 3.—Photograph of kidney (Case 3) showing cortical congestion and numerous small haemorrhages with sparser larger haemorrhages in the medulla.

Blood examination gave the following results;

> Haemoglobin, 38 per cent. (Sahli); erythrocytes, 1·6 million per c.mm.; leucocytes, 24,600 per c.mm.; reticulocytes, 16 per cent.; urea nitrogen, 265 mg. per cent., an extremely high figure.

Slight generalized muscular twitchings were observed at 6.30 p.m. By evening so little fluid had been retained and so much lost in the diarrhoeal stools that, in spite of the lack of apparent dehydration, an intravenous drip was begun. Half-strength Hartmann's solution containing 5 per cent. glucose (1 oz. per hour) was given for three and a half hours followed by whole blood (¾ oz. per hour) for three hours. The general condition steadily deteriorated. Penicillin, 100,000 units intramuscularly four-hourly, was given on this, the last day of the illness.

Death occurred at 2 a.m. on July 19, 1948.

NECROPSY (performed nine hours after death). The body was that of a well developed, well nourished infant. The skin was pale. No pitting oedema was found, but the subcutaneous tissue generally was very wet.

The pleural and pericardial sacs each contained about 50 ml. and the peritoneal cavity about 100 ml. of clear yellow transudate.

The only organs showing gross abnormality were the kidneys. These were of identical appearance (fig. 3); they were considerably swollen; the subcapsular surface was smooth, congested, and stippled with tiny haemorrhages; on section, both cortex and medulla were greatly congested, swollen and soft; the cortex showed numerous tiny petechiae, and the medulla fairly frequent, considerably larger, haemorrhages. No focal areas of infarction were seen. The pelves appeared healthy. The bladder was empty.

The lungs showed considerable oedema and hypostatic congestion. The myocardium and the liver were pale.

The bone marrow of the middle of the shaft of the femur appeared of the uniform red colour to be expected at this age.

Brain and meninges, middle-ear cavities, mouth, neck organs, stomach and bowel, biliary passages, pancreas, suprarenals, spleen, uterus, tubes, and ovaries all appeared normal.

On histological examination both kidneys showed a picture basically identical with that seen in Case 1; great engorgement and thrombosis of glomeruli with patchy necrosis of cortical tubules (fig. 4). Nearly all the glomeruli showed great congestion of some or all of their capillary loops, and many loops were occluded by fibrin thrombi. In some cases a part or the whole of the glomerulus was fused into a fibrinoid necrotic mass. In the less damaged glomeruli there was swelling and proliferation of the tuft epithelium and some of the cells showed eosinophil colloid droplet degeneration; a few glomeruli showed capsular 'crescent' formation. The capillary endothelium showed swelling, fatty degeneration and proliferation in some glomeruli; some capillary loops were (in contrast to the majority) ischaemic through this proliferation. These proliferative changes were most marked in the juxta-medullary glomeruli, which tended to be less severely affected than the others.

The tubular necrosis was, as in Case 1, patchy

and limited to the cortex; some patches showed complete infarction, the interstitial cells as well as the tubular epithelium being necrotic; other patches showed necrosis of all the tubules with survival of the interstitium, whereas in others only the proximal convoluted tubules were necrotic. Proximal tubules which had escaped necrosis showed colloid droplet change and fatty degeneration. There were many glomerular haemorrhages, extending into the corresponding proximal tubules. Red cells were seen also in many loops of Henle and distal convoluted tubules, but only occasionally in collecting tubules.

The patches of necrosis were much more sparsely placed than in Case 1, although the glomerular lesion was equally severe. It was noticeable that tubular necrosis occurred, especially in those areas where the ratio of volume of glomerular to tubular tissue approached that of the adult kidney; areas where the relative underdevelopment of tubular tissue, characteristic of the infantile kidney, was marked, tended to escape tubular necrosis.

The medulla showed no necrosis. Many tubules contained casts, mainly hyaline. There were occasional interstitial haemorrhages.

Many afferent arterioles were plugged by fibrin thrombi, apparently extending back from the associated glomeruli; occasionally the thrombosis extended back into an interlobular artery. Some afferent arterioles and interlobular arteries showed fatty degeneration of the muscle and endothelium, and fibrinoid infiltration of the intima, or even fibrinoid necrosis of the wall. This change was seen sometimes without thrombosis of the vessel. These vessels were not appreciably dilated. The larger arteries and veins appeared normal. There was no thrombosis of vessels in the medulla.

Slight polymorph infiltration was seen in some of the necrotic foci.

There was a little fatty degeneration in the liver, indiscriminately distributed through the lobules. There was no necrosis or vascular thrombosis.

The small intestine was normal.

Marrow from the middle of the shaft of the femur showed congestion and gross hypoplasia with a normal erythroid : leukoblastic ratio. Plasma cells were considerably increased.

Sections of the spleen, lung, myocardium, pancreas, and suprarenal showed no abnormality.

Case 4. G.P., a male infant., aged nine weeks (61 days) at death, was admitted to the Gastro-enteritis Unit, City Fever Hospital, Edinburgh, on Feb. 17, 1948, with a history of vomiting for fourteen days and diarrhoea for nine days.

This infant was born in the Simpson Maternity Hospital, Edinburgh, on Jan. 5, 1948, of an unmarried mother. (Birth weight, 7 lb. 1 oz.) He progressed satisfactorily for four weeks. Two weeks before admission he began to vomit after feeds. Diarrhoea began five days later. One week before admission to hospital the feeding was changed from fresh cows' milk to National Dried Milk. The weight, which had stood at 7 lb. 3 oz. for a fortnight, fell 11 oz. in the last week before admission.

After two weeks of illness the infant was taken to the Medical Out-Patient Department at the Royal Hospital for Sick Children, Edinburgh, where he was found to be in a marasmic state, and was then admitted to the Gastro-Enteritis Unit at the City Fever Hospital.

On admission the infant was slightly toxic looking,

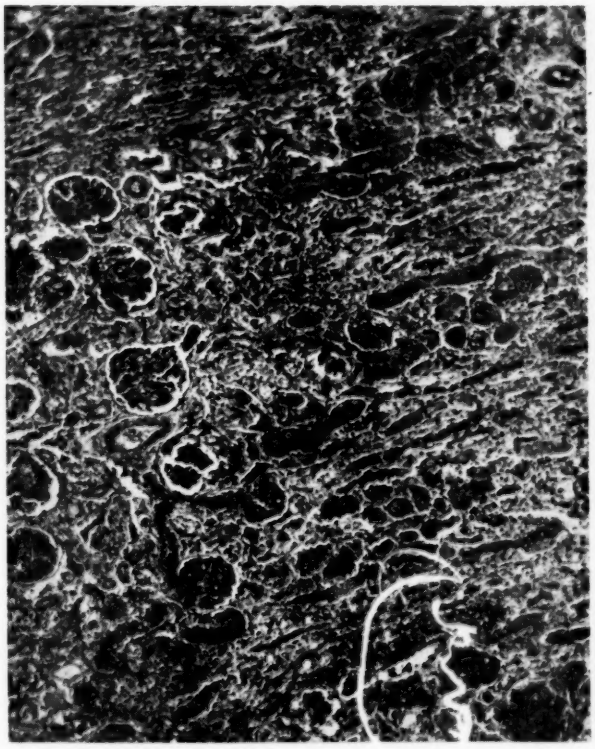

FIG. 4.—Photomicrograph of renal cortex (Case 3) showing glomerular congestion and thrombosis, thrombosis of two afferent arterioles, and several patches of tubular necrosis (dark staining). Haematoxylin and eosin. ×70.

and weighed 6 lb. 15 oz. Skin hydration was fair. The eyes were not sunken, nor was the anterior fontanelle depressed. The mouth was clean and moist. The ears looked healthy. Nothing abnormal was found in the chest or abdomen.

On the first day in hospital there was occasional vomiting and the stools were green and watery. Urine was passed freely. Gastric lavage yielded clear fluid with a little mucus. Hartmann's solution, half-strength, 3 oz., three-hourly by mouth, was given, and also potassium citrate, gr. 5, and sulphadiazine 0·25 g., four-hourly.

On Feb. 18, 1948, the general condition was fair.

Oedema of the eyelids was noticed. Urine examination showed:

> No albumin; no cells; film, no organisms seen; culture, scanty growth of B. Proteus.

A rectal swab did not grow any pathogens.

On Feb. 19 the vomiting had ceased and the stools were reduced in number and were firmer in consistence. The oedema was worse and had spread to the hands and feet. The abdomen had become distended and cyanosis of the trunk and lower limbs had developed. Urine was still being passed freely; it did not contain albumin and the chloride content was 2 g. per litre. A rectal swab did not grow any pathogens. A very dilute 'special Cow and Gate half-cream' feed was begun, also 'betaxan' vitamin B complex, 1 ml. intramuscularly, daily.

On Feb. 20 the general condition was fair, and feeding satisfactory. A rectal swab did not grow any pathogens.

On Feb. 21 the oedema had become worse. There was considerable pitting, even over the front of the chest, and the extremities were swollen and blue. Urine was being passed but the amount was not estimated.

On Feb. 23 urine examination (catheter specimen) showed:

> Film, no pus cells, a few Gram-positive cocci; culture, a scanty growth of enterococci.

The general condition remained unchanged until Feb. 25, when the breathing became rapid and laboured. The temperature reached 99·8° F. after having been slightly elevated on the previous day, but by Feb. 26 the temperature had returned to normal. The oedema had subsided. The infant weighed 6 oz. less than on admission. Sulphadiazine was stopped after 15 g. had been given over a period of nine days. 'Betaxan' was also discontinued.

On Feb. 27 the infant continued to feed well, but the stools had again become loose and rather frequent. The infant had lost 1 lb. over the last four days. There was no evidence of infection. The ears appeared to be healthy.

On Feb. 29 a moderate degree of oedema had returned.

On Mar. 1 the infant was feeding well, and passing urine. The oedema was unchanged. The ears appeared healthy. By Mar. 3 the oedema had subsided, but the weight was ½ lb. less than a week earlier when there was no oedema. The infant continued to pass urine. A cough had developed.

The Half Cream Dried Milk was discontinued and replaced by breast-milk and 5 per cent. glucose water in equal parts, with the addition of half a drachm of 'hepovite' to each feed of 3½ oz. given three-hourly. But on Mar. 5 general deterioration had occurred. The infant continued to pass urine. The temperature, which had been steadily rising for three days, reached 100·4° F. The ears appeared healthy. An intravenous drip of plasma and 5 per cent. glucose in equal parts was begun, also penicillin 50,000 units six-hourly and sulphadiazine 0·25 g. four-hourly. On the following day the general condition had deteriorated rapidly. The temperature remained at 100° F. and the child was gravely ill. The abdomen had become distended and the liver was enlarged to three finger-breadths below the costal margin. Jaundice was observed in the evening. The last nursing record of the passage of urine was at 10 a.m. It was probably impossible to distinguish between urine-staining of the napkin and that caused by the loose yellow stools passed on this and the previous day, so it was not possible to be sure when urine was last passed. Pink staining of the napkin attributable to urine was not recorded on any occasion.

Death occurred at 12.10 a.m. on Mar. 7, 1948.

NECROPSY (performed thirty-nine hours after death). The body was that of a male infant, slightly undersized, and considerably wasted. The skin showed moderate jaundice, but no petechiae. The fontanelle was sunken, but there was slight oedema of the dorsum of hands and feet. The serous sacs contained no excess of free fluid.

The small intestine showed mucosal petechiae, very sparse in the upper part, but fairly numerous in the lower ileum. The colon showed slight congestion and oedema of the mucosa, with occasional small petechiae.

The liver was slightly pale.

The left middle-ear cavity contained thick yellow pus, smears of which showed organisms resembling pneumococci and coliform bacilli; culture yielded Bact. coli only.

The lungs showed numerous pleural petechiae; the posterior parts of both lower lobes showed congestion, slight oedema, and a fine nodularity indicating early bronchopneumonia.

The heart showed numerous epicardial petechiae, and occasional petechiae within the substance of the left ventricular myocardium.

The kidneys were of identical appearance: they were moderately swollen and soft, the cortex tending to tear on stripping the capsule; the surface was smooth and pale, with scanty petechiae; on section, the cortex was swollen, pale, and sparsely studded with tiny petechiae; the outer zone of the medulla also appeared pale.

The other organs appeared normal.

Histological examination of both kidneys showed the same picture (figs. 5 and 6). The most striking changes were in the glomeruli, almost every one of which was involved; they showed gross dilatation of their capillary loops, some by close-packed red cells, and some by fibrin thrombi. The lesion appeared to be an early one; there was no sign of necrosis of the glomerular cells, nor was there any endothelial or epithelial proliferation or swelling, or polymorph infiltration. Many of the afferent arterioles were also affected, showing dilatation and profuse infiltration of red cells into their walls; a few were plugged by fibrin thrombi. The larger

vessels appeared normal. The tubules showed very much less severe changes than in Cases 1 and 3. Apart from cloudy swelling (difficult to assess in view of the long interval between death and necropsy) there was hyaline droplet change in some of the proximal convoluted tubules, and occasional small groups of these tubules showed early coagulative necrosis. There were, rather remarkably, no red cells in capsular spaces or tubular lumina. The interstitial tissue of the cortex showed oedema and occasional small haemorrhages. The medulla appeared normal.

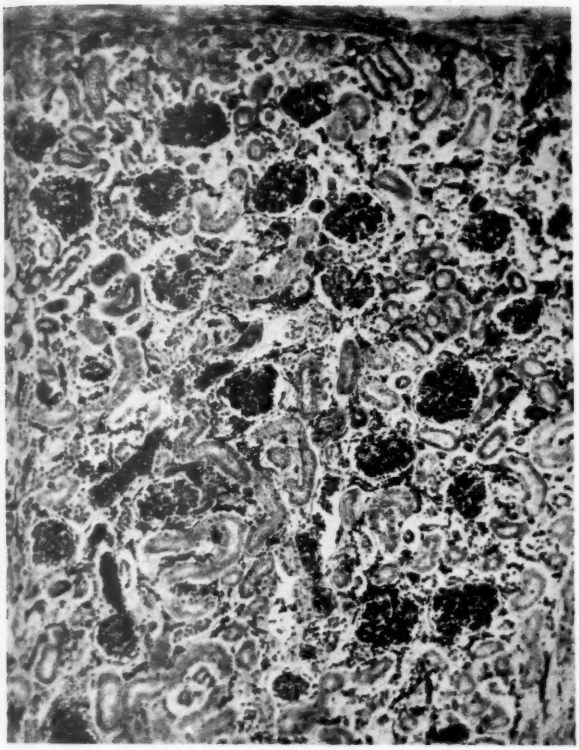

FIG. 5.—Photomicrograph of renal cortex (Case 4) showing great glomerular congestion and thrombosis. The fibrin thrombi appear black and the red cells almost black. Phosphotungstic acid haematoxylin. ×70.

The liver showed occasional small areas of focal necrosis, haphazardly located in the lobules. There was some histiocytic proliferation in these foci.

In the small and large intestine there were a few small mucosal haemorrhages, but no inflammatory changes.

The lower lobe of the lung showed acute bronchiolitis and early bronchopneumonia, with a little patchy collapse.

The mesenteric lymph nodes, spleen, pancreas and myocardium showed no significant abnormality.

Summary of the Pathological Changes in the Kidneys

The renal lesion appears to be of the same type in the four cases, varying only in degree and age. It is symmetrical renal cortical necrosis, or, as it has been called by Dunn and Montgomery (1941), acute necrotizing glomerulonephritis. The essential change appears to consist of vasostasis in the glomeruli, followed by ischaemic necrosis of the cortical tubules, and to a varying degree of the interstitial tissue also, produced by the failure of their blood supply from the efferent arterioles. Sometimes large patches of complete necrosis of all elements of the cortex may be seen. In other cases or in other parts of the same kidney the necrosis may be limited to the tubular epithelium, or may be still more limited, affecting only the proximal convoluted tubules (that part of the kidney tissue which is most vulnerable to ischaemia, as can be seen at the margins of the ordinary embolic infarct). None of the cases showed the classical macroscopic picture of patches of frank yellow infarction of the cortex. It is, however, well recognized that this is not constant, and in Cases 1 and 3 the microscopic picture entirely conformed to established criteria. In both, cortical tubular necrosis was extensive. The diagnosis of

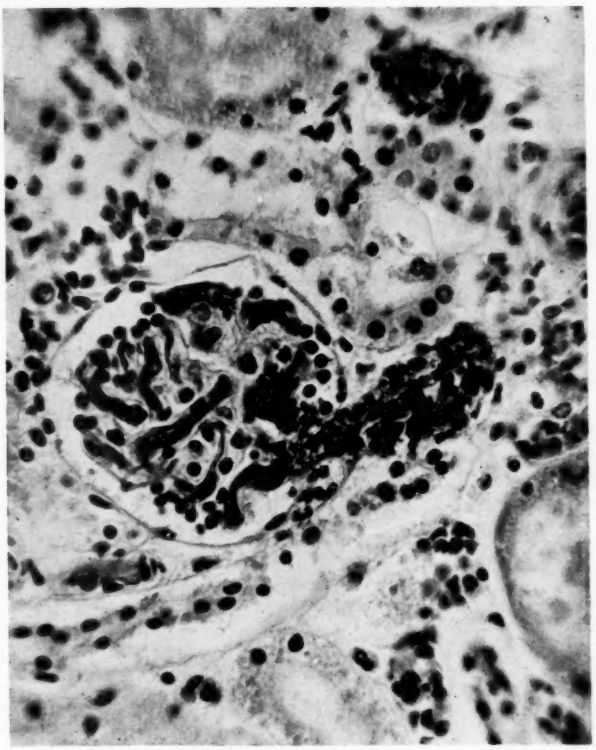

FIG. 6.—Photomicrograph of same section of renal cortex as in Fig. 5, showing in detail a typical glomerulus with capillaries blocked by fibrin thrombi. Note the infiltration of red cells into the wall of the afferent arteriole. Phosphotungstic acid haematoxylin. ×400.

renal cortical necrosis is not as obviously justified in Cases 2 and 4 where there was much less tubular necrosis. But in Case 4 at any rate this may well be due to the cortical ischaemia being of too short a duration to have produced histologically appreciable necrosis in many tubules. If we accept cortical vasostasis as the prime factor in the production of the lesion, the evidence of widespread glomerular stasis in Case 4 justifies the inclusion of this case in the same category as Cases 1 and 3. The stasis was so severe that a considerable degree of tubular necrosis must inevitably have developed had the child lived a little longer. It is significant that in this case, where the clinicians' attention had been focussed on renal function by the earlier occurrence of oedema, apparently normal urine is known to have been passed at least up till two days before death, thus supporting the view that the renal lesion was recent.

In Case 2 also the degree of frank necrosis was slight in comparison with Cases 1 and 3, though the glomerular lesion appeared similar in type and severity to that in the other cases. Here again it may be that the relative slightness of tubular necrosis was due to a short duration of the vascular upset; a point in favour of this is the absence of proliferative changes in the less damaged glomeruli in contrast to Cases 1 and 3. The considerable polymorph infiltration in and around the cortical tubules, on the other hand, suggests a lesion of longer duration; from analogy with the changes in infarcts in other organs (for example, the heart) one would not expect marked polymorph infiltration to appear in under twenty-four hours, by which time necrosis should be histologically obvious. It is possible, however, that the vascular upset may initially have been insufficient to produce frank tubular necrosis, but sufficient to produce emigration of leucocytes from the semi-static intertubular capillaries (the stage of leucodiapedesis or perileu-

PRINCIPAL CLINICAL FEATURES IN THIRTEEN CASES OF SYMMETRICAL CORTICAL

Year	Authors	Age (in years)	Sex	Associated Infection	Anuria (Days Complete)	Abnormal Urine	Renal Pain
1913	Herzog	10	F.	Peritonitis (cryptogenic)	?	?	?
1915	Zanzig	14	F.	Pneumonia	4	+	?
1925	Fahr	4	M.	?	?	?	?
1925	Fahr	?	?	?	?	?	?
1928	Apert and Bach	13½	M.	Pulm. tuberculosis Rhinopharyngitis	2	+	?
1933	Von Zalka	13	F.	Acute tonsillitis	10	+	+
1937	Bell	9	M.	Pneumonia; empyema	+	?	?
1941	Dunn and Montgomery	9	M.	Acute tonsillitis (Scarlet fever)	6	?	?
1941	Dunn and Montgomery	8	F.	?	4	?	+
1949	Authors' Case I	10½	F.	Intestinal tuberculosis	3	+	–
1949	Authors' Case II	4½	F.	Streptococcal septicaemia Arthritis : ? Meningitis	?	?	?
1949	Authors' Case III	5½ months	F.	Rhinopharyngitis 'Gastroenteritis'	?	?	?
1949	Authors' Case IV	9 weeks	M.	Gastroenteritis Otitis media Bronchopneumonia	1	?	?

costasis in Ricker's (1921) schema of abnormal states of blood flow). After this change had been present for a day or more the vascular upset may have then become more severe, with more or less complete glomerular stasis, not present long enough to make the resultant tubular necrosis obvious in its full extent. Some degree of tubular necrosis was certainly present.

It may be objected that the well marked polymorph infiltration in Case 2 reflects not ischaemic damage, but a reaction to blood-borne infection. Haemolytic streptococci were isolated from the leptomeninges, and Gram-positive cocci were certainly present in the kidney sections, but they were found only in small groups within vascular lumina, without obvious reaction around them, indicating post-mortem growth of organisms present in the blood at death. None was found in the interstitial polymorph infiltrations. Further, the fact that polymorph infiltration was entirely absent from the medulla, though marked in the cortex, speaks strongly against a pyaemic infection of the kidney. It is unfortunate that the clinical record gives no help in assessing the duration of the renal lesion in this case; but severe diarrhoea came on suddenly four days before death, and there are grounds for believing that the renal and bowel lesions in such cases as this are contemporaneous.

Clinical Features

The principal clinical features in the thirteen cases of bilateral cortical necrosis of the kidneys in children under fifteen years of age are shown below. The symptoms are essentially the same as in adults. Unfortunately, most of the clinical records are incomplete. Fairly detailed clinical data are available in seven cases, those of Apert and Bach (1928), von Zalka (1933), two cases of Dunn and Montgomery (1941), and three of our cases.

NECROSIS OF THE KIDNEYS IN CHILDREN UNDER FIFTEEN YEARS OF AGE

Nitrogen Retention	Blood Pressure	Oedema	Coma	Convulsions	Vomiting	Diarrhoea	Melaena	Various
?	?	?	?	?	+	?	?	
?	?	?	?	?	+	?	?	
?	?	?	?	?	?	+	?	
?	?	?	?	?	?	+	?	
Urea 290 mg. %	?	+	?	–	+	+	?	Epistaxis
N.P.N. 324 mg. %	100 mm. Hg	–	–	+	+	?	?	
Urea N. 182 mg.	120 mm. Hg	–	?	?	?	?	?	
Urea 230 mg. %	140/80 mm. Hg	+	–	–	?	?	?	
?	?	–	–	–	?	+	?	
Urea N. 130 mg. %	120/70 mm. Hg	–	+	+	+	+	+	
?	?	?	?	?	?	+	?	
Urea N. 265 mg. %	?	+	–	+	+	+	+	Hypo-plastic anaemia (severe)
?	?	+	–	–	+	+	–	

Fragmentary clinical notes are available in four cases, those of Herzog (1913), Bell (1937), Zanzig (1915), and one of our cases. No clinical notes are available in Fahr's (1925) two cases. Fahr described the pathology in the case of a boy of four years without giving any clinical data, and he mentioned having also seen a case in another child with 'dysentery.'

Infection. This was a feature in nine of the thirteen cases, and it may have been present in some of the other four. It was acute in seven patients, five of whom had a severe infection, and chronic in two.

Severe acute parenteral infection was a feature in five patients; three had acute haemolytic streptococcal infection, one had pneumonia, and one had pneumonia followed by empyema. Acute rhinopharyngitis was observed in our Case 3 on the day on which diarrhoea with melaena developed and eight days before death from renal failure. Apert and Bach's patient who had pulmonary tuberculosis developed rhinopharyngitis sixteen days before the detection of the urinary disturbance. Infective gastro-enteritis appeared to be the cause of the diarrhoea and deterioration in health which developed one month before death in our Case 4.

Chronic infection in the form of tuberculosis was a feature in two cases. One had a pulmonary infection and the other an intestinal infection. The tuberculous process in the latter case was relatively inactive (Case 1).

Infective enteritis was presumed in three patients of the series of thirteen. Fahr's two children were said to have 'dysentery', and our 5½ months' old infant 'gastro-enteritis.' But the diarrhoea in these cases may not have had an infective origin, since diarrhoea, which is sometimes associated with melaena, is a common feature in patients with symmetrical cortical necrosis of the kidneys (Cases 1 and 3). Enteritis was not presumed in the second case of Dunn and Montgomery, 'a girl of eight years, previously quite healthy, who had a sudden attack of diarrhoea while out walking and developed anuria on the same day.' Such a history is more suggestive of a common cause for both the diarrhoea and the anuria than of an infective enteritis.

Urine. Attention was first drawn to the urinary abnormality by the development of oliguria, anuria, or haematuria, usually one of the first two. Abnormal urine, containing blood and albumin, was usually not observed until a small amount of urine was obtained by catheterization. In the six cases in which particulars about the urine are available the duration of anuria varied from two to ten days with an average of five days. In the two infants recorded in this paper it was not possible to be sure of the presence of anuria since both had diarrhoea, but oliguria was undoubtedly present (Cases 3 and 4). Data regarding urine examination are available in three cases. All showed haematuria and heavy albuminuria.

Renal pain. Pain in the kidney region was noted in two cases. Apparently it was not a notable feature in the other four cases with a reasonable history, although, of course, children often do not complain of pain.

Nitrogen retention. Blood nitrogen estimations were done in six cases and all showed very high levels. The figures varied from urea 230 mg. per cent. to urea nitrogen 265 mg. per cent.

Blood pressure. This was estimated in four cases. It was normal in one, slightly elevated in two and considerably elevated in one.

Oedema. This feature was present in four and not apparent in four cases.

Headache. This symptom was not mentioned in any case, but it may, nevertheless, have occurred since children usually do not complain of it.

Coma. The sensorium remained clear in five cases until death, but one child developed coma on the day before death.

Convulsions. Fits or muscular twitchings were observed in three of the seven cases with a fairly detailed history. Our patient aged 10½ years developed major convulsions with coma the day before death. Von Zalka's patient died in a terminal convulsion. In this disease convulsions are a grave sign and indicate impending death.

Vomiting. This was a feature in seven cases, including our infant who suffered from gastro-enteritis.

Diarrhoea. This symptom occurred in eight cases, including our infant with gastro-enteritis and Fahr's two cases about which no other clinical facts are known.

Melaena. Blood was observed in the stools in two of the six cases with diarrhoea in which there is a reasonable history (our Cases 1 and 4). It began at the same time as the diarrhoea in our patient of 10½ years in whom there was no evidence of alimentary infection other than healing tuberculosis. It also occurred on the first day of illness and diarrhoea in our 5½-months-old infant who was thought to be suffering from gastro-enteritis. The occurrence of alimentary haemorrhage in renal cortical necrosis seems worthy of emphasis in view of the probability that it is of similar pathogenesis to the renal lesion.

Discussion

The renal lesion. The pathogenesis of symmetrical renal cortical necrosis has been fully discussed by numerous authors, notably Scriver and Oertel (1930), Dunn and Montgomery (1941), and Duff and More (1941). It is generally agreed that the essential feature is reduction or cessation of blood flow through the glomeruli, the necrosis following as a result of the ischaemia of the cortex thus produced. Many of the earlier authors laid stress on the primary rôle of thrombosis, but others have, in our opinion, correctly, regarded it as secondary to stasis. And in some cases (Dunn and Montgomery, 1941; Duff and More, 1941) the

degree of thrombosis has been inadequate to explain the widespread stasis.

Those who discard thrombosis as the primary phenomenon postulate various functional vascular disturbances as the cause of the stasis. Dunn and Montgomery suggested that the primary fault is a dilatation of the glomerular capillaries, either from toxaemia of some kind or from anoxia associated with general hypotension; this dilatation produces excessive glomerular filtration, which raises the viscosity of the blood within the capillaries to such a degree that glomerular stasis occurs. The dilatation and the various structural changes found in the afferent arterioles and interlobular arteries are, in their opinion, secondary, being due to the rise of pressure in these vessels following occlusion of the related glomerular capillary bed. They supported this conception by the fact that the glomerular capillaries are unique among capillaries because of their normal function of filtration, whereas the renal arteries and arterioles are functionally similar to those of other organs. It is not, however, safe to assume that the renal arteries and arterioles behave as do those of other organs; the work of Lauson, Bradley, and Cournand (1944), Corcoran, Taylor, and Page (1943), and Trueta and his fellow workers (1947) indicates an especial tendency of the renal arteries to very active constriction under certain circumstances. Further, the associated lesions found fairly frequently in other organs in cases of cortical necrosis strongly suggest in our opinion a pathogenesis similar to that of the renal lesions; and the capillary bed of these organs does not share the peculiar function of the glomerular capillaries.

Scriver and Oertel (1930), also, explained the production of the lesions by a process of vascular dilatation with resultant stasis, without, however, limiting the primary vascular change to the glomeruli. They applied to the pathogenesis of the cortical necrosis the concept of Ricker and his school (Ricker and Regendanz, 1921). This concept, based on direct observation of the vascular reactions to various stimuli in experimental animals, implies that small arteries and capillaries respond to stimuli of varying intensity by a series of different reactions, namely, (*a*) dilatation with acceleration of the stream; (*b*) constriction with slowing; (*c*) great dilatation with, eventually, slowing and perhaps complete stasis, the slowing and stasis being due to constriction of the arteries proximal to the strongly stimulated area. Stasis, during which the red cells become packed together, but not necessarily thrombosed, may be reversible. The stages of dilatation with sluggish flow which may precede or follow stasis are both described as peristasis. During this stage of peristasis diapedesis of red cells and leucocytes may occur, though not at the same point in the stage. This concept does not seem to have attracted the interest it deserves among British pathologists. It has been criticized, notably by Tannenberg (1925), who stressed the importance of chemical changes in the irritated tissue, producing a local sedimenting tendency of the intravascular red cells and thereby leading to stasis without necessarily any change in vascular calibre. Such local chemical changes would also cause leucocytic emigration by chemotaxis.

Much of Tannenberg's criticism appears valid. But the experimental observation of graded vascular reactions on the lines of Ricker's concept remains, and there are certainly lesions in human pathology where primary vascular dysfunction seems most probable, complicated no doubt by secondary effects produced by extravascular chemical change. Renal cortical necrosis seems to be such a lesion. Whether the pattern of vascular change fits in to the grading of Ricker's concept is, however, another matter.

Scriver and Oertel explained the changes in cortical necrosis on the basis of Ricker's thesis. They postulated a vasoparalysis, with great vascular dilatation, affecting the ' terminal arterial segments ' (the smallest arteries, the arterioles, and the arterial capillaries), ' to which is generally added narrowing in the course of the preceding proximal artery.' The resultant stasis leads to necrosis. The leucocytic emigration, which may be present both in the non-necrotic and the necrotic areas of the cortex, occurs during the preceding stage of peristasis. They did not believe that vasospasm was the primary disturbance; the capillary congestion and red cell diapedesis were, in their opinion, too pronounced.

It has long been known that renal cortical necrosis can be produced in rabbits by the administration of staphylococcal toxin. De Navasquez (1938) investigated this rabbit lesion. He believed that the earliest change was great vascular dilatation of the interlobular arteries and afferent arterioles. This led to a rise of pressure in the glomerular capillaries producing increased glomerular filtration, red cell concentration in the capillaries, conglutination, and stasis. This theory has much in common with that of Dunn and Montgomery, but locates the primary vasodilatation in the arteries and arterioles rather than in the glomerular capillaries.

Other workers (Jardine and Teacher, 1911 ; Ash, 1933; Hertig and Mallory, 1946; and others) believe that the primary disturbance is spasm of renal arteries or arterioles. This gains experimental support from the work of Byrom (1937) who produced similar renal lesions in rats by injections of vasopressin; in these experiments marked focal blanching of the surface of the kidneys was seen shortly after injection. Byrom described the widespread cortical necroses he produced as anaemic infarcts, but he noted that some capillaries showed dilatation. It is difficult to say from his description whether glomerular capillary dilatation was present to a degree sufficient to make his lesions entirely comparable to human cortical necrosis.

The vasospastic theory is strongly supported by the fact that very active arterial contraction is a notable characteristic of the kidneys under various pathological conditions. Corcoran, Taylor, and Page (1943), and Lauson, Bradley, and Cournand

(1944) have shown, in the dog and in man respectively, that in traumatic shock the effective renal blood flow is reduced out of proportion to the degree of hypotension, and may remain reduced though the blood pressure has been restored to normal. In heart failure, with reduced cardiac output, Mokotoff, Rose, and Leiter (1948) have shown that effective renal blood flow is reduced to a much greater extent than the cardiac output, indicating greater vasoconstriction in the kidneys than in the body as a whole.

Trueta and his fellow workers (1947) have demonstrated this renal vasoconstrictor phenomenon with great precision in the rabbit. They have shown that various stimuli will cause a shunting of the renal blood flow away from the cortex, making it almost medullary, apparently by intense vasoconstriction of the distal parts of the interlobular arteries. The route of the medullary flow is through the juxta-medullary glomeruli, supplied from the proximal parts of these arteries. They suggested that renal cortical necrosis in man may be due to a prolonged and exaggerated version of this shunt phenomenon. They emphasized the striking fact that in the human lesion not only is the medulla spared the necrosis that devastates the cortex, but also the juxta-medullary glomeruli are much less severely affected than those throughout the rest of the cortex. And they have shown that staphylococcal toxin, notorious as a means of producing cortical necrosis in the rabbit, calls the medullary shunt into action. On direct inspection, the surface of the rabbit's kidney was seen to blanch shortly after the intravenous injection of the toxin.

Duff and More (writing in 1941, before the publication of the monograph of Trueta and his fellow workers) attempted to resolve the conflict between the vasoparalytic and vasospastic theories by a compromise. They postulated a state of excessive sensitivity of renal arteries and arterioles in those individuals who develop cortical necrosis. Various stimuli may then produce in these hypersensitive vessels a series of vascular disturbances of increasing severity: intense vasospasm, vasoparalysis, damage to the arterial walls either from the vasospasm or from direct action of some toxic substance. At any stage in this sequence blood flow may be halted, either from thrombosis, or blood stasis and conglutination following vasoparalysis, or from intense vasoconstriction alone.

This interpretation seems to explain the lesion most satisfactorily, provided that (especially in view of the work of Byrom and of Trueta et al.) we accept spasm of the interlobular arteries as the essential initial phenomenon. By the time the patient dies these vessels, as well as the afferent arterioles and the glomerular capillaries, usually appear to be in a state of vasoparalysis. This is probably due to anoxic damage to the vessel walls incurred during the initial vasoconstriction, reinforced perhaps by a toxin, though in some cases evidence of a primary toxaemia is singularly lacking. Probably the factor, stressed by De Navasquez (1938) and by Dunn and Montgomery (1941), of excessive glomerular filtration, leading to increased viscosity of the blood in the glomerular capillaries, plays a part in the final production of glomerular stasis. If arterial vasospasm passes off blood will re-enter glomeruli whose capillaries, damaged by the period of vasospastic anoxia, will presumably allow excessive filtration to take place, until the capillary flow is brought to a standstill by red cell conglutination or thrombosis.

Dunn and Montgomery regarded thrombosis of renal veins as another mechanism capable of producing the lesion. They cited cases recorded by Torrens (1911), Herzog (1913), and Fahr (1925). But analysis of these records does not suggest that the lesions present were really examples of symmetrical renal cortical necrosis. Herzog and Fahr described necrosis in the medulla as well as the cortex in their cases, which in our opinion eliminates them from this category. In the case reported by Torrens the histological description given is too brief to permit of its proper classification.

Lesions in other organs. These fall into two groups, 'associated lesions,' apparently contemporaneous with that of the kidneys, and probably produced by a similar mechanism, and 'background lesions' indicating pre-existing diseases of which the renal cortical necrosis may have been a complication.

ASSOCIATED LESIONS. The lesions in our cases which may be regarded as contemporaneous were the haemorrhagic necrosis of the ileum in Case 1 and of the colon in Case 2, and the focal necroses of the liver in Case 4. Both have been previously described in the literature of symmetrical renal cortical necrosis. Haemorrhagic and necrotizing lesions of the alimentary tract have been recorded with rather striking frequency, in the oesophagus (Weaver and von Haam, 1939), stomach (Herzog, 1913), small intestine (zu Jeddeloh, 1932), and colon (Jardine and Teacher, 1911; Herzog, 1913; Bamforth, 1923; Scriver and Oertel, 1930; Dunn and Montgomery, 1941; Sheldon and Hertig, 1942) And in other cases, 'dysentery' or 'bloody diarrhoea' has been noted clinically, without mention being made of the state of the bowel at necropsy. In some of these cases it has been suggested either that the bowel lesion has been the primary one, later causing the renal cortical necrosis, or that the bowel lesion has been a 'uraemic colitis' following the establishment of renal failure. It is difficult to eliminate either of these hypotheses from the published data of the individual cases, but in some at least the history is more suggestive of a simultaneous onset of the lesions in kidneys and bowel. Certainly in Case 1 of our series this appeared to be so; anuria was observed on the morning after the onset of bloodstained diarrhoea, and microscopically the ages of the renal lesion and the haemorrhagic enteritis appeared similar.

The fact that the bowel lesions appear to have arisen simultaneously with those in the kidneys suggests that they are of similar pathogenesis; that is, due to local vascular disturbance. This is borne out pathologically. In our Case 1 the patches of 'enteritis' showed a predominance of necrosis and vascular change, (congestion, oedema, haemorrhage, and thrombosis), over leucocytic reaction. In Case 4 the appearance of the lesion of the colon was that of a massive haemorrhagic infarction suggesting a thrombosis of the inferior mesenteric artery, but no such thrombosis could be found. Arterial vasospasm would seem to be the most probable basic factor in the production of these lesions, as of those in the kidneys.

Our fourth case showed small focal necroses in the liver. These also have been recorded not infrequently (Bamforth, 1923; von Zalka, 1933; Garvin and Van Wezel, 1938; Weaver and von Haam, 1939; Sheldon and Hertig, 1942; Brown and Crane, 1943). These focal necroses have been described variously as centrilobular, central and midzonal, diffuse, or typically eclamptic. In our case they were haphazard. Microscopically they appeared to be contemporary with the renal lesion. Their haphazard distribution can, in our opinion, best be explained on a basis of local arteriolar spasm. Focal necroses due to toxaemia or to generalized anoxia or ischaemia should have shown a more constantly zonal distribution. The development of jaundice in this case the day before death suggests a degree of liver failure greater than could be explained by the focal necroses alone; these were sparse, and the total amount of liver tissue involved must have been trivial. We have no means of knowing whether the jaundice was due to widespread ischaemia of the liver, produced by extensive arterial or arteriolar spasm, reaching an intensity sufficient to produce necrosis only in the territories of a few arterioles; to ischaemia from general hypotension; to some hypothetical toxaemia; or to prolonged nutritional deficiency. The liver showed no histological signs of diffuse damage, such as fatty degeneration.

Other organs have been noted in the literature of cortical necrosis as showing lesions such as might well have been produced by arterial or arteriolar spasm. Focal necroses have been reported in the adrenals (Jardine and Teacher, 1911; Evans and Gilbert, 1936; Weaver and von Haam, 1939; Sheldon and Hertig, 1942; Hertig and Mallory, 1946); in the spleen (Geipel, 1925; Scriver and Oertel, 1930); in the pancreas (French, 1940); and in the hypophysis (Sheldon and Hertig; Doniach and Walker, 1946). The hypophyseal necroses occurred in cases complicating pregnancy, and may be explained as examples of the lesion found not uncommonly in the post-partum state. Apart from these lesions in the hypophysis, the associated lesions have been confined to and distributed widely through the splanchnic vascular bed.

These associated and probably contemporaneous lesions merit more attention than they have received, since they may play a considerable part in, or even dominate, the clinical picture. In our Case 1 the bowel lesion was the first sign of catastrophe, and in Case 2 it was of such severity that it must almost certainly have caused symptoms, though the clinical notes unfortunately give inadequate details of the terminal illness. In Case 4 liver damage rather than kidney damage marked the onset of the terminal syndrome, since jaundice developed whereas no urinary disturbance was noted.

We suggest, therefore, the concept of a 'syndrome of splanchnic vasospasm,' rather than one of a purely renal disturbance. It is convenient to use the designation 'symmetrical renal cortical necrosis,' since the renal lesion appears to be a constant part of the syndrome, and may be the only obvious component. But the wider concept should be borne in mind, since both clinically, and macroscopically at necropsy, the renal lesion may not make itself obvious in early cases, or may be overshadowed by other components of the syndrome.

BACKGROUND DISEASES. Infection which could be presumed to antedate the renal lesion was present in three of our own four cases (see table). It was of varying kind and degree: most severe in Case 2 (haemolytic streptococcal arthritis and septicaemia); fairly severe in Case 4 (infantile gastro-enteritis, purulent otitis media, and broncho-pneumonia); and mild in Case 1 (abdominal tuberculosis of low grade activity). In Case 3 rhinopharyngitis was noted at the onset of the illness, but this appeared to be an insignificant infection. The clinical diagnosis of gastro-enteritis appears doubtful; blood in the stools was noted on the first day of diarrhoea, which is unusual in true infective infantile gastro-enteritis. It seems probable that the 'enteritic' symptoms were due to minor vasospastic incidents in the bowel, contemporaneous with, rather than causing, the renal lesion. The significance of the hypoplastic anaemia which was present in this case is not clear. We have no evidence that it antedated the renal lesion. It may be, therefore, that this case falls into the idiopathic group (vide infra).

In the other cases in childhood which we have briefly reviewed (see table) infection was present in most, but again it was of varying type and severity. In the two cases reported by Fahr as complicating 'dysentery,' the bowel lesion may well have been contemporaneous with that of the kidneys, both being components of a splanchnic vasospastic syndrome.

A review of the adult cases in the literature shows a remarkable diversity of background diseases. Termination of pregnancy, usually complicated by eclampsia, or retroplacental haemorrhage, or both, stands out as the commonest cause. Another large group has been associated with infections of various kinds. A miscellaneous group has been associated with such diverse conditions as myocardial infarction (von Zalka, 1933), traumatic shock (Furtwängler,

1927; McFarlane, 1941), burns (Brown and Crane, 1943), polyarteritis nodosa (Mallory, 1947), carcinoma of ureter (Dunn and Montgomery, 1941), carcinoma of prostate (Weber, 1909; Fahr, 1925), and poisoning by dioxan (Barber, 1934), and almond extract (Garvin and Van Wezel, 1938). A few cases have occurred without evidence of any primary disease (Ash, 1933; Garvin and Van Wezel, 1938; personal observation (Campbell, unpublished). In the case attributed by French (1940) to acute pancreatitis, it seems possible that this condition, regarded as primary, was in fact an associated contemporaneous lesion rather than the cause of the renal lesion.

Dunn and Montgomery suggested that two main factors could be extracted from the diverse etiological background: (1) an acute fall in blood pressure, and (2) a toxic factor, bacterial or otherwise. They stressed the hypotension or relative hypotension produced by the occurrence of retroplacental haemorrhage in the previously hypertensive eclamptic woman, the usual background of the pregnancy cases. We do not agree with their theory that these factors act primarily on the glomerular capillaries, but the two factors do appear to be the most probable etiological common denominators. In those cases complicating infections bacterial toxaemia may be postulated as the prime cause, whereas in some at least of the miscellaneous group acute hypotension seems to be responsible (for example, the cases complicating myocardial infarction, traumatic shock and burns). In view of the work of Trueta et al. (1947), Corcoran et al. (1943), and Lauson et al. (1944), both these factors seem capable of calling into action renal cortical vasospasm, and the simultaneous vasospasm which we believe may occur in other parts of the splanchnic vascular bed.

The idiopathic cases remain unexplained. As Duff and More emphasized, an essential factor in the etiology of the condition appears to be an unusual degree of sensitivity of the renal cortical vessels. Renal cortical necrosis occurs in only a small proportion of those individuals who suffer from the various primary diseases recorded. In certain individuals the sensitivity of the renal cortical arteries appears to be so great that a stimulus too slight to be associated with any obvious primary disease may call the renal medullary shunt into violent and prolonged action.

Special features in childhood. From our review of the literature there is no doubt that renal cortical necrosis, which is fairly rare in adults, is also rare in children. No definite cases have previously been recorded in infants, though two doubtful examples have been mentioned: the first was an infant aged 11 months, briefly mentioned by Fahr (1925), and not identified by him as renal cortical necrosis; the second was an infant aged 3½ months, mentioned by Bell (1937). In a brief note on this infant Bell reported a renal lesion characterized by widespread thrombosis of afferent arterioles. The state of the tubules was not mentioned. He did not classify this case as symmetrical cortical necrosis, though he noted its resemblance to the case of Juhel-Rénoy. It may possibly belong to this category, but satisfactory classification is impossible in the absence of sufficient detail. It seems to us that in infancy the lesion may occasionally be missed. Clinically, oliguria or anuria are less obvious in the napkin period, and pathologically, the renal lesion (our Case 4) may not be macroscopically striking at this age. Furthermore, the peculiarities of the infant kidney may modify the pathological lesion to a much less florid picture. In our Case 4, despite gross glomerular stasis, tubular necrosis was inconspicuous. This may have been merely a matter of the immaturity of the lesion. But in infancy, tubular development lags anatomically behind glomerular development, and the work of McCance (1946) and Dean and McCance (1947) suggests that in this age period tubular function also lags behind that of the glomeruli. The relatively undeveloped tubules of the infant kidney may well be less vulnerable to ischaemia than those of the kidney whose function has achieved the adult pattern, and tubular necrosis may therefore tend to be less conspicuous in the infant. Nevertheless, that it can occur on a large scale as early as five months, is shown by our Case 3.

The acute pneumococcal nephritis reported by Blackman and Rake (1932) as occurring especially in infants has certain resemblances to the lesion of renal cortical necrosis. These authors found fibrin and hyaline thrombosis constantly in the glomeruli, with a varying amount of necrosis of tubular epithelium. In many of their cases the changes appear to have been too slight to justify the assumption of the severe degree of glomerular stasis which is characteristic of renal cortical necrosis, but some cases at least suggest a mild form of that lesion. Indeed, it seems probable that from time to time cases, both in children and in adults, have been labelled 'acute thrombotic nephritis' or 'acute haemorrhagic nephritis' which in essence have been cases of symmetrical renal cortical necrosis.

Summary

The clinical and pathological features of symmetrical renal cortical necrosis in childhood have been reviewed.

Four personal cases are described, including two cases in infants, the first to be recorded in this age period. Nine other cases occurring in children under fifteen years of age have been found in the literature, and have been reviewed.

The clinical features of the disease in childhood are similar to those of cases in adult life. Anuric or oliguric renal failure is the predominant feature. But the occurrence of vascular disturbances in other parts of the splanchnic vascular bed is emphasized,

notably in the bowel; diarrhoea, with or without passage of blood, is a frequent symptom. The renal lesion is regarded as the predominant feature of a splanchnic vasospastic syndrome.

We are indebted to Dr. Alexander Joe for permission to use the clinical records of two cases, and to Mr. T. C. Dodds for the photographs.

References

Apert, M. E., and Bach, E. (1928). *Bull. mém. Soc. méd. hôp. de Paris*, **52**, 471.

Ash, J. E. (1933). *Amer. J. med. Sci.*, **185**, 71.

Bamforth, J. (1923). *J. Path. Bact.*, **26**, 40.

Barber, H. (1934). *Guy's Hosp. Rep.*, **84**, 267.

Bell, E. T. (1937). *Amer. J. Path.*, **13**, 497.

Blackman, S. S., and Rake, G. (1932). *Bull. Johns Hopk. Hosp.*, **51**, 217.

Brown, C. E., and Crane, G. L. (1943). *J. Amer. med. Ass.*, **122**, 871.

Byrom, F. B. (1937). *J. Path. Bact.*, **45**, 1.

Corcoran, A. C., Taylor, R. D., and Page, I. H. (1943). *Ann. Surg.*, **118**, 871.

Dean, R. F. A., and McCance, R. A. (1947). *J. Physiol.*, **106**, 431.

De Navasquez, S. (1938). *J. Path. Bact.*, **46**, 47.

Doniach, I., and Walker, A. H. C. (1946). *J. Obstet. Gynaec.*, **53**, 140.

Duff, G. L., and More, R. H. (1941). *Amer. J. med. Sci.*, **201**, 428.

Dunn, J. S., and Montgomery, G. L. (1941). *J. Path. Bact.*, **52**, 1.

Evans, N., and Gilbert, E. W. (1936). *Amer. J. Path.*, **12**, 553.

Fahr, T. (1925). *Henke and Lubarsch's Handbuch der speziellen pathologischen Anatomie und Histologie*, vol. VI/I, pp. 132, 140, and 143. Berlin. Springer.

French, R. W. (1940). *Amer. J. Surg.*, **47**, 666.

Furtwängler, A. (1927). Quoted by Duff and Murray.

Garvin, C. F., and Van Wezel, N. (1938). *Arch. intern. Med.*, **62**, 423.

Geipel, P. (1925). *Arch. Gynäk.*, **124**, 231.

Hertig, A. T., and Mallory, T. B. (1946). *New Engl. J. Med.*, **234**, 416.

Herzog, G. (1913). *Beitr. path. Anat.*, **56**, 175.

Jardine, R., and Teacher, J. H. (1911). *J. Path. Bact.*, **15**, 137.

Juhel-Rénoy, E. (1886). *Arch. gén. Méd.*, **17**, 385.

Lauson, H. D., Bradley, S. E., and Cournand, A. (1944). *J. clin. Invest.*, **23**, 381.

Mallory, T. B. (1947). *New Eng. J. Med.*, **236**, 670.

McCance, R. A. (1946). *Schweiz. med. Wschr.*, **76**, 857.

McFarlane, D. (1941). *J. Path. Bact.*, **52**, 406.

Mokotoff, R., Ross, G., and Leiter, L. (1948). *J. clin. Invest.*, **27**, 1.

Ricker, G., and Regendanz, P. (1921). *Arch. path. Anat.*, **231**, 1.

Scriver, W. de M., and Oertel, H. (1930). *J. Path. Bact.*, **33**, 1071.

Sheldon, W. H., and Hertig, A. T. (1942). *Arch. Path.*, **34**, 866.

Tannenberg, J. (1925). *Frankfurt. Z. Path.*, **31**, 173, 182, 285, 351 and 385.

Torrens, J. A. (1911). *Lancet*, **1**, 99.

Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L. (1947). *Studies of the Renal Circulation*. Oxford. Blackwell.

Von Zalka, E. (1933). *Arch. path. Anat.*, **290**, 53.

Weaver, R. G., and von Haam, E. (1939). *Arch. intern. Med.*, **63**, 1084.

Weber, F. P. (1909). *Lancet*, **1**, 601.

Zanzig, T. (1915). Quoted by Duff and Murray.

zu Jeddeloh, B. (1932). *Arch. path. Anat.*, **286**, 389.

MILIARY SEBACEOUS CYSTS AND BLISTERS IN THE HEALTHY NEWBORN

BY

ISRAEL GORDON, M.D.(Ed.), M.R.C.P.(Lond.), D.P.H.
Deputy Medical Officer of Health, Ilford

Miliary sebaceous cysts and blisters are probably the commonest neonatal skin disorder (if disorder it be), yet there has apparently been no reference to it in the periodical medical literature of the last thirty-two years, and it is ignored in many textbooks of dermatology and poorly described in others. Warvi and Gates (1943) do not mention the condition in a survey of epithelial cysts. Unna (1896) in his textbook showed the lesions to be sebaceous cysts, and the glands to be hypertrophic and occluded by a thin horny layer. In Macleod's 'Diseases of the Skin' (1933) the association with the sebaceous glands is also mentioned. So far as I am aware, the 'blister' form has not been described before, nor the actual incidence.

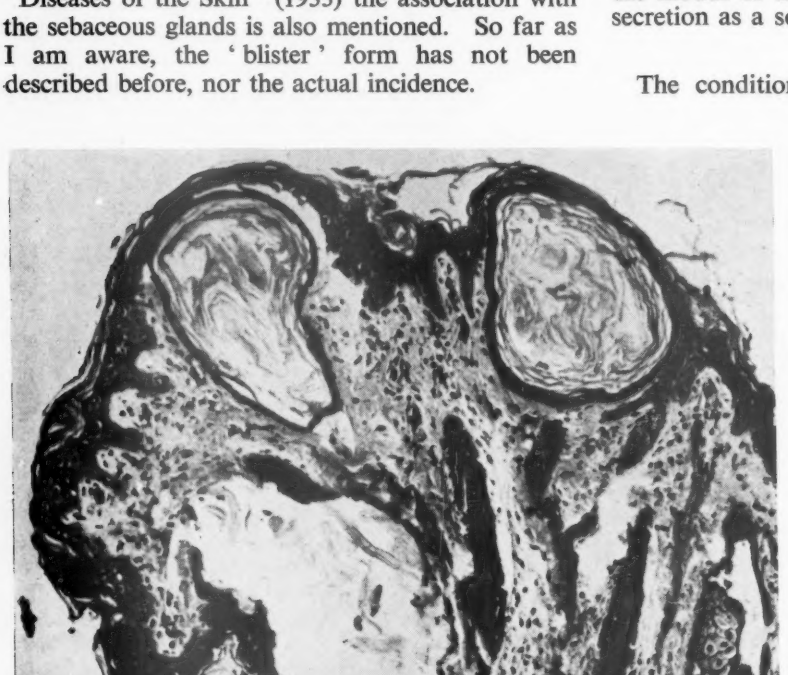

FIG. 1.—Miliary sebaceous cysts. × 100.

Appearance

The spots are pearly white, about the size of the head of a pin or somewhat smaller. They occur on the cheeks, chin, naso-labial folds, and forehead, and in marked cases may even be found on the upper half of the trunk. There may be only one or two or a dozen or more. Some are in the skin, others are raised above it and superficial. Occasionally one may cap a red papule. Microscopically there appear to be two forms, a typical small sebaceous cyst in the dermis (fig. 1), and a superficial type where the horny layer seems to have overgrown the mouth of the duct and has been raised by the secretion as a sort of sebaceous blister (fig. 2).

Incidence

The condition apparently arises in foetal life. The spots were present in thirty-nine out of one hundred infants examined in the first twenty-four hours after delivery. In the first four weeks of life they were present in sixty out of one hundred and forty-eight infants (41 per cent.); in the second four weeks in thirty-nine out of one hundred and six infants (37 per cent.); in the third four weeks in ten out of forty-eight infants (21 per cent.); and then the incidence drops sharply, the spots being present only in seven out of one hundred and eight infants (6 per cent.) in the second three months of life. Some of the spots seem to be absorbed, others, presumably the superficial ones, dry up and drop off. Similar lesions are found occasionally in adults, who may have a tendency to develop these milia, of an ephemeral nature. I have not included the appearance found in the skin of the tip of the nose of the newborn child in these figures. A white speckling is seen here in nearly all infants, is always deep in the skin, and is presumably the same condition. In the small series available there

was no difference between breast and bottle fed babies of any statistical significance.

Papules on the face are very common in the first few months of infant life. Their incidence, however, differs altogether from these sebaceous lesions. At birth they were found in only three out of one hundred, in the second month in fifty-seven out of one hundred and six (54 per cent.); thereafter the incidence diminished gradually. Occasionally there may be a cyst or a blister capping a papule, in which case the lesion resembles a small pustule.

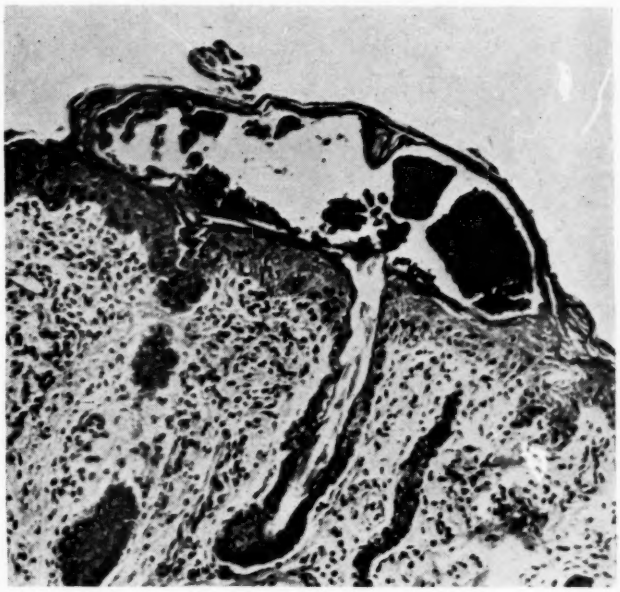

FIG. 2.—Miliary sebaceous blister. × 100.

Discussion

That cyst formation in the sebaceous glands begins in foetal life has been shown by Reiss (1932). He states that in the foetus these glands reach a high level of functional activity and excrete so abundantly that the sebum cannot all escape from the ducts, and cyst formation begins. He asserts that the vernix caseosa is partly formed by the secretion of these glands, hence their activity. Macleod (1933) states that they are retention cysts caused by the plugging of a dilated duct by debris. It is easily apparent that in the neonatal form no such plugging takes place as the cyst is capped by a shiny uniform patch of epidermis. It does appear that the glands are highly developed in foetal life, probably to help to form the vernix caseosa, but eventually the normal skin grows over the ducts of many of the glands, thus closing them. Further secretion ensues and a cyst forms.

Sutton (1939), discussing these milia in adults, mentions that in many cases there is a history of excessive drinking of milk. I have corroborated this in some cases, if fat-eating be added to milk-drinking. Even in these times of rationing some people with sufficient desire for fat can obtain extra quantities. The secretion of the sebaceous glands contains much cholesterol (Reiss, 1932; Montagna and Noback, 1947); lanolin, an analogous excretion, is similarly largely constituted of cholesterol. Milk contains much cholesterol; the human infant, in fact, weight for weight, ingests an amount of cholesterol almost comparable to that given to experimental rabbits, in whom hypercholesterolaemia and atheroma results. In fact Kube and Ssolowjew (1930) found that lipoid deposition in the intima of aortae of infants did begin to occur shortly after birth and attributed this to the high cholesterol diet. The amount of cholesterol in the nutriment the foetus obtains from the mother is of course unknown, but Wislocki and Bennett (1943) state that cholesterol does pass the placenta, in contradistinction to neutral fat, which probably does not. It seems not improbable then that the foetus has a high level of cholesterol metabolism, when endogenous production is considered as well. The fact that the serum cholesterol of the newborn is low (60 mgm. per cent., Hueper, 1945), probably means that it is utilized as quickly as it is delivered, so it cannot accumulate in the blood, as it begins to do shortly after birth. Perhaps one way in which it is used up is in the formation of a sebaceous secretion to be passed in the vernix caseosa.

Summary

1. Approximately 40 per cent. of healthy newborn infants present milia, mainly on the face.

2. These milia are miliary sebaceous cysts and blisters, and have probably resulted from the epidermis overgrowing the ducts of sebaceous glands.

3. In foetal life the sebaceous glands are highly active, perhaps to help to form the vernix caseosa.

4. The incidence of these cysts and blisters gradually diminishes, and becomes negligible by the second three months of life.

5. There may be some relationship between activity of these sebaceous glands and cholesterol metabolism.

The work for this paper was carried out in the infant welfare centres and Maternity Home of the borough of Ilford, and for facilities there I am indebted to Dr. J. H. Weir.

REFERENCES

Hueper, W. C. (1945). *Arch. Path.*, **39**, 187.
Kube, N., and Ssolowjew, A. (1930). *Frankfurt. Z. Path.*, **40**, 302.

Macleod, J. M. H. (1933). 'Diseases of the Skin.' London.
Montagna, W., and Noback, C. R. (1947). *Amer. J. Anat.*, **81**, 39.
Reiss, H. (1932). *Arch. Derm. Syph. Wien*, **166**, 30.
Sutton, R. L., and Sutton, R. L., Jr. (1939). 'Diseases of the Skin.' St. Louis.
Unna, P. G. (1896). 'The Histopathology of the Diseases of the Skin.' Edinburgh.
Warvi, W. N., and Gates, O. (1943). *Amer. J. Path.*, **19**, 765.
Wislocki, G. B., and Bennett, H. S. (1943). *Amer. J. Anat.*, **73**, 335.

A STUDY OF TEN CHILDREN AFTER TREATMENT WITH STREPTOMYCIN FOR TUBERCULOUS MENINGITIS

BY

JOHN LORBER, M.B., B.Chir., M.R.C.P.
(From the Department of Child Health, University of Sheffield)

Following the discovery of streptomycin by Waksman (1944) and his colleagues, great hopes were entertained that its use in cases of tuberculosis, and especially of tuberculous meningitis, would be followed by results equally dramatic and good as those with penicillin in pyogenic infection in general and the pyogenic meningitides in particular. These hopes were engendered by the excellent experimental results in guinea-pigs achieved by Feldman and Hinshaw (1944), but the first few reports of cases of tuberculous meningitis treated by streptomycin were so discouraging that opinion swung the other way. Of Hinshaw's (1946) first four living cases after relatively short periods of follow-up, one was blind, one deaf, one ataxic, and one was still being treated. Cooke's (1946) patient who recovered was left with 'nervous and mental changes.' Krafchik's (1946) case was apparently well after a very short follow-up.

The general impression was expressed in the following annotation in the 'British Medical Journal' late in 1946:

'The results of American and limited British tests of streptomycin in tuberculous meningitis have, in particular, been far less encouraging than was originally hoped; there seems to be a very real risk that, even if the infection is controlled (as has only very rarely happened) the patient will usually be left mentally deficient, deaf, blind, or otherwise a hopeless invalid.'

Later publications (Alperin and Toomey, 1948; American Trudeau Society, 1947 and 1949; Applebaum and Halkin, 1947; Bunn, 1948; Cathie, 1949; Choremis, 1948; Debré et al., 1948; Decourt, 1948; Dolivo and Rossi, 1948; Dowling, 1949; Dubois, 1948; 'Lancet,' 1948a and 1948b; McDermott, 1947; Mann, 1948; Medical Research Council, 1948; Mordasini, 1948; Nau, and Wenzler, 1948; and Rubie and Mohun, 1949) produce an over-all impression that when tuberculous meningitis is treated with streptomycin most patients die, and that of the minority who survive a considerable number are deaf or paralysed, and others are mentally abnormal. Smith et al. (1948), and Lincoln and Kirmse (1949) on the contrary, point out that recovered cases have not been left badly crippled either physically or mentally.

Material of Present Study

Between September, 1947, and July, 1948, twenty-seven patients suffering from tuberculous meningitis were treated in the Streptomycin Unit of the Department of Child Health, University of Sheffield, under the direction of Professor R. S. Illingworth. Of these sixteen died and one is alive, but is still having treatment. The remaining ten cases are the material of the present study, and they satisfy the following criteria.

Each patient has been followed up for a minimum of ten months, from the beginning of treatment to the end of May, 1949. (See table 1.)

TABLE 1

AGES ON ADMISSION AND LENGTH OF FOLLOW-UP

Case	Sex	Age on Admission in years	Length of Follow-up in Months	
			Beginning of treatment to May 31, 1949	End of treatment to May 31, 1949
1 (L.M.)	M.	$6\frac{8}{12}$	20	16
2 (P.F.)	M.	$1\frac{3}{12}$	19	12
3 (J.H.)	F.	$5\frac{8}{12}$	19	8
4 (K.E.)	F.	$6\frac{9}{12}$	17	4
5 (E.R.)	M.	$\frac{11}{12}$	15	8
6 (G.H.)	F.	$8\frac{3}{12}$	14	10
7 (G.R.)	M.	$3\frac{6}{12}$	14	6
8 (D.C.)	M.	$1\frac{2}{12}$	13	7
9 (C.W.)	F.	$5\frac{6}{12}$	12	6
10 (J.D.)	F.	8	10	4

The cerebrospinal fluid is normal in every case. Tubercle bacilli were found in each case. Organisms of the human type were isolated from all patients though not necessarily from the cerebrospinal fluid in patients with miliary tuberculosis as well as meningitis.

Each child is now at home.

All the children are reporting monthly to a special follow-up clinic.

In six of these ten cases miliary tuberculosis was also present at the beginning of treatment, but the patients are now radiologically clear of miliary lesions. None of the ten patients was unconscious before or during treatment and none had convulsions. All had intrathecal treatment. In the only case in this series (G.H.) in which air encephalography was performed (eight months after treatment started) the ventricular system was found to be normal.

Three of these children were under two years of age on admission.

Method of Investigation

The physical state of the children is assessed by a monthly routine examination, which includes weighing, x-ray scrutiny of the chest and, less often, investigation of the cerebrospinal fluid.

Their behaviour is noted and enquiries are made about their behaviour at home. Where practicable some have been visited and observed in their homes.

Intellectual achievements are also noted, and in all cases of school age reports are obtained from the school about their previous behaviour and mental development. In addition, every case undergoes psychometric testing some time after the conclusion of treatment and where necessary the tests are repeated at a later date.

In children over five the Terman-Merrill 'L' scale (a modified Stanford-Binet scale), and in children of pre-school age the Gesell test with some Terman-Merrill items, were used for measuring intelligence. In one case (K.E.) a special set of tests for the deaf was selected (Collins-Drever battery). Table 2 shows the method employed in each case and the results.

Wherever possible the general family background is also reviewed to place each case in a better perspective.

Interpretation of Results of Psychometric Tests

Although these tests were designed to eliminate as much as possible the influence of experience and education, nevertheless the absence of normal home life and schooling for up to a year or more must to some extent adversely influence the results. Further, it was not always possible to gain the full co-operation of all the children, especially toddlers, partly because of their recent memory of injections and other therapeutic procedures.

The delay in development, which was marked in the younger age groups, can be largely ascribed to their prolonged stay in hospital. That this is so is shown by the very rapid improvement in their achievements after only a short period at home. The acquisition of speech and sphincter control is particularly difficult in hospital.

These factors must be taken into consideration in the assessment of the results obtained, but when the tests are repeated after a longer follow-up they will be eliminated.

Case Reports

Case 1. L.M., aged eight years and one month, an only child, is a sturdy, well-built boy in perfect physical health.

TABLE 2

METHODS AND RESULTS OF INTELLIGENCE TESTS

Case	Age in years	Mental age in years	I.Q.	Method employed	Co-operation
1 (L.M.) ..	a. $7\frac{11}{12}$	$6\frac{4}{12}$	80	Terman-Merrill	Negative
	b. $8\frac{1}{12}$	$6\frac{8}{12}$	82	,, ,,	,,
2 (P.F.) ..	a. $2\frac{7}{12}$	$2\frac{8}{12}$	87	Gesell	Good
	b. $2\frac{9}{12}$	$2\frac{3}{12}$	82	,,	,,
3 (J.H.) ..	$6\frac{10}{12}$	$4\frac{11}{12}$	72	Terman-Merrill	,,
4 (K.E.) ..	$7\frac{6}{12}$	$10\frac{1}{12}$	135	Collins-Drever	,,
5 (E.R.) ..	a. $1\frac{11}{12}$	$1\frac{6}{12}$	78	Gesell	Poor
	b. 2	2	100	,,	Good
6 (G.H.) ..	$9\frac{1}{12}$	$7\frac{10}{12}$	86	Terman-Merrill	Good
7 (G.R.) ..	a. $4\frac{2}{12}$	$3\frac{9}{12}$	90	Combined Gesell-Terman-Merrill	,,
	b. $4\frac{6}{12}$	$4\frac{6}{12}$	100	,, ,, ,,	,,
8 (D.C.) ..	a. $2\frac{8}{12}$	$1\frac{8}{12}$	74	Gesell	Inattentive
	b. $2\frac{5}{12}$	$2\frac{8}{12}$	93	,,	Good
9 (C.W.) ..	$6\frac{3}{12}$	6	96	Terman-Merrill	,,
10 (J.D.) ..	$8\frac{8}{12}$	$9\frac{4}{12}$	108	,, ,,	,,

He was always a shy, taciturn child, lacking in confidence. He had little to say while he was in hospital but was always well behaved as he is now. He is attending school, but unfortunately he derives less benefit from this than he should, as he is placed in a form with boys of his own age. Because he missed a whole year he cannot catch up with the others, and this makes him still more diffident. This behaviour was reflected in the results of his two intelligence tests performed within two months. His I.Q., 80 and 82 at the two tests respectively, was felt to be an underestimate of his true ability and his various failures were probably due not so much to inability to perform some of the test items, as to a negative attitude to the test situation.

Case 2. P.F., aged two years and nine months, is the younger of two boys. He is in fine physical health. The last radiograph of his chest shows a healed fibrotic lesion at one apex at the site of his original primary focus.

His parents are sensible, ordinary people, except that the mother suffers from attacks of hysteria.

The boy is active, interested in everything, friendly and happy, giving much pleasure to his parents and friends. Although he was very backward on his discharge from hospital, he is picking up rapidly and can do most things a child of his age should do. According to his parents he is more intelligent than his elder brother.

He was very co-operative at his first psychometric test, performed three months after his discharge home. There was some scatter, but his general level was between 24 and 30/12, and his I.Q., 87. The second test was performed two months later. His mother was present at the beginning of the test, but had to be removed on account of an attack of hysteria. The child, nevertheless, co-operated quite well, but showed no change in the previous level attained.

Case 3. J.H., a girl aged six years and ten months, comes from a very dull family and is the first of two children. Her mother in particular is a woman of very low intelligence, completely unreliable, and emotionally unstable.

This child is in very good health, is usually active and happy, but her behaviour is very much like her mother's as she is emotional and sometimes difficult to control at home. In this respect she is no different from what she has always been and she never did well at school.

Her intelligence behind a bright façade is obviously low. At her psychometric test she co-operated well, but her I.Q. was only 72. Though she had virtually no schooling it was not felt in this case that lack of experience of normal life materially affected the test result though this factor cannot be ruled out entirely.

Case 4. K.E., a girl of seven and a half years, is an only child of bright, intelligent parents, and before her illness was always very forward.

Physically she is perfectly fit, but is unfortunately deaf. She had one relapse of meningitis, but following a second course of treatment the cerebrospinal fluid has now been normal for six months.

Emotionally she is labile, and, while most of the time she is charming, she has temper tantrums. This is probably due to the newly acquired deafness and the difficult situations to which this gives rise. That her illness is not likely to have diminished her mental capacity was shown at her psychometric test (Collins-Drever battery) which gave a figure of 135. This test was performed a month before discharge from the convalescent home. She is being given lessons in lip-reading and now that she can understand better what other people say, the temper tantrums have decreased.

Case 5. E.R., a boy aged two years, is an only child of an intelligent mother and a less intelligent father, situated in very poor circumstances. He is a very friendly, happy boy, not afraid of strangers at home, although he was shy and reluctant to co-operate in tests at the hospital. At his first psychometric test at the hospital, a year after his admission, his I.Q. was 78 only. This was felt to be an underestimate of his real development. The next test was therefore performed at his own home, and here he showed himself to be fully equal to the mental standard of his chronological age, and his I.Q. was 100. In the bulk of the test items there was little scatter, but in a few respects a wide divergence from the average was noted in each direction.

Case 6. G.H., a girl aged nine years and one month, is one of four children in a very poor home. The father deserted the family, and the mother, though trying to do her best for the family, is of low intelligence. This child was retarded before her illness. For example, she could not walk unaided until sixteen months.

She is in good physical health and is perfectly normal emotionally though her interests are rather limited. Her psychometric measurement gave an I.Q. of 86 which is a true mirror of her present mental ability.

Case 7. G.R., a boy of three years and five months, is the second child of an average father and an intelligent mother. The mother and several members of the family on her side are extremely highly strung people. Her father committed suicide in a paroxysm of anxiety, and the mother herself appears to be suffering from an acute anxiety state. In spite of that, she is a good and careful mother.

The child shows constant activity, is alert and keen, always at the centre of attraction, and a general favourite. In most respects he knows much more now than children of his age, especially in memorizing figures and difficult names. At his first psychometric test before his discharge from hospital he showed considerable fluctuation in achievement, surpassing his age in memory tests but falling short in picture identification and other items where his lack of experience hindered him. His I.Q. was only 90 on this occasion.

Three months later he was re-tested and this time

he again proved to be well above the average in certain items, though below it in tests involving motor functions. With this scatter above and below his chronological age his I.Q. came to 100. There seems to be little doubt that he will do better in time.

Case 8. D.C., a boy of one year and two months, comes from an average family and has one elder brother. He developed normally until his illness. He is now well but still has a large opacity in his lung which remained practically unchanged during treatment.

The child is active and playful, but was obviously much below the general level of mental development for his age at the time of the first psychometric test, performed just before his discharge. Co-operation in the test was patchy, but his I.Q. of 74 was probably accurate. He was particularly defective in speech and toilet habits. At a re-test, two months later at his own home, he showed considerable improvement. He was interested and co-operative. By now he was 'dry,' could speak in three-word sentences, knew a nursery rhyme, and was in general of a higher intellectual development than his elder brother of three and a half who was tested at the same time. His present I.Q. is 93.

Case 9. C.W., aged six years and three months, is an only daughter of average parents. Before her illness she was a very bright child and was thought to be exceptional by her mother. Although she only attended school for four weeks, her teacher remembers her as a child of great intelligence and of a happy and quiet disposition. In hospital she was always very quiet.

She is now physically perfectly fit. She co-operated well in her psychometric test, performed just before her discharge from hospital, and her I.Q. was 96. According to her mother, she is not quite so bright as she was before her illness. The school report corroborates the mother's estimate of her previous mental level, which though fully up to average now, may have fallen.

Case 10. J.D., eight years and eight months old, is the younger of two girls and has bright intelligent parents. She is in perfect physical health and has a most attractive personality. She is interested in everything around her and is pleasant to all. Although rather nervous at first during her intelligence test, she did well and her I.Q. of 108 may be higher after a period at home.

Of these ten children, five boys and five girls, comprising all the cases of a consecutive series who are alive after the completion of their treatment with streptomycin for tuberculous meningitis, nine have no physical disabilities attributable either to the disease or to its treatment. One child is deaf, possibly permanently, although a short time ago she could hear a very loud noise for the first time.

In no case have the parents noted any change in the behaviour of the child following the disease and its treatment. There is only one mild behaviour problem (case 3).

The range of the intelligence quotients of these children, tested between eight and eighteen months after the beginning of treatment, and in no case less than two months after the end of treatment, is between I.Q. 72 and 135. This is within the normal range of variation in the general population. The number of cases is far too small for statistical analysis. Smith et al. (1948) obtained similar results in their recovered cases.

These results do not confirm the many pessimistic opinions about the outcome of tuberculous meningitis. It is true that serious sequelae may result from the disease or its treatment but in our experience they are infrequent.

Summary

The physical and mental state and the emotional pattern of ten children successfully treated with streptomycin for tuberculous meningitis have been analysed. All the children are now at home and have been followed up for at least ten months from the beginning of treatment, and for four to sixteen and a half months after the treatment completed by the end of May, 1949.

All the children are in good physical health and are normal mentally. There is no evidence that the illness has caused any difference in their general behaviour. The intelligence quotients are within the normal range of variation.

The only neurological after-effect is deafness in one case.

All the children were alive and well at the end of July, 1949, after a minimum observation period of one year from the beginning of treatment.

These cases were treated under the Streptomycin Investigation Scheme of the Ministry of Health.

Thanks are due to Mr. N. E. Whilde, school educational psychologist, Sheffield, for his collaboration with the psychometric tests in the school-age children, to Sir Weldon Dalrymple-Champneys, Bart., for his permission to publish, and to Sister Farrow and her nurses for their part in achieving these results.

I should especially like to thank Professor R. S. Illingworth for his constant help, encouragement, and criticism.

References

Alperin, L., and Toomey, J. A. (1948). *J. Pediat.*, **33,** 74.
American Trudeau Society (1947). *Amer. Rev. Tuberc.*, **56,** 477.
—— (1949). *Ibid.*, **59,** 106.
Annotation (1946). *Brit. med. J.*, **2,** 906.
Appelbaum, E. and Halkin, C. (1947). *J. Amer. med. Assoc.*, **135,** 153.
Bunn, P. A. (1948). *Amer. J. med. Sci.*, **216,** 286.
Cairns, H., and Taylor, M. (1949). *Proc. R. Soc. Med.*, **42,** 155.

Cathie, I. A. B. (1949). *Lancet*, **1**, 441.
Choremis, K., Zervos, N., Constantinides, V., and Pantazis, S. (1948). *Lancet*, **2**, 595.
Cooke, R. E., Dunphy, D. L., and Blake, F. G. (1946). *Yale J. Biol. Med.*, **18**, 221.
Debré, R., Thiefry, S., and Brissaud, H. E. (1948). *La Streptomycine appliquée au traitement de la méningite tuberculeuse et de la tuberculose miliaire chez l'enfant. Paris.* 182-189.
Decourt, J., Guillemin, J., Canivet, J., Sibertin-Blanc, J., Jupeau, M., Villiaumey, J., and Chevance, L. G. (1948). *Pr. Med.*, **56**, 128.
Dolivo, G., and Rossi, E. (1948). *Streptomycin und Tuberkulose*, edited by Fanconi, G., and Löffler, W. Basel.
Dowling, H. F., Sweet, L. K., Hirsh, H. L., and Lepper, M. H. (1949). *J. Amer. med. Assoc.*, **139**, 755.
Dubois, R., Linz, R., Leschanowski, H., Schlesser, R., and Wattiez, R. (1948). *Acta clin. belg.*, **3**, 1.
Editorial (1947). *Amer. Rev. Tuberc.*, **56**, 442.
—— (1948a). *Lancet*, **1**, 217.
—— (1948b). *Ibid.*, **1**, 291.
Feldman, W. H., and Hinshaw, H. C. (1944). *Proc. Mayo Clin.*, **19**, 593.
Hinshaw, H. C., Feldman, W. H., and Pfuetze, K. H. (1946). *J. Amer. med. Ass.*, **132**, 778.
Lincoln, E. M., and Kirmse, T. W. (1949). *Lancet*, **1**, 767.
Mann, T. P. (1948). *Proc. R. Soc. Med.*, **41**, 671.
McDermott, W., Muschenheim, C., Hadley, S. J., Bunn, P. A., and Gorman, R. V. (1947). *Ann. Intern. Med.*, **27**, 769.
Mordasini, E. (1948). *Schweiz. med. Wschr.*, **78**, 605.
Medical Research Council (1948). *Lancet*, **1**, 582.
Nau, O. S., and Wenzler, F. J. (1948). *J. Pediat.*, **3**, 410.
Rubie, J., and Mohun, A. F. (1949). *Brit. med. J.*, **1**, 338.
Schatz, A., Bugie, E., and Wakeman, S. A. (1944). *Proc. Soc. exp. Biol.*, **55**, 66.
Smith, H. V., Vollum, R. L., and Cairns, H. (1948). *Lancet*, **1**, 627.

THE PHYSICAL AND MENTAL DEVELOPMENT OF CHILDREN WITH CONGENITAL HEART DISEASE

BY

MAURICE CAMPBELL, O.B.E., D.M., F.R.C.P., and GEOFFREY REYNOLDS, B.M., B.Ch.,
(From the Cardiac Department, Guy's Hospital, London)

Many children with congenital heart disease are obviously thin and under weight and some are small for their age. This has been commented on by many writers but there are few studies of any large series.

Benn (1947) has analysed statistically the height and weight of school children with patent ductus arteriosus. He found both boys and girls were under weight, the differences for the boys being probably, and for the girls certainly, of statistical significance. The increased height of the girls also seemed to be of statistical significance. In auricular septal defect, under-development and small build were emphasized by Roesler (1934) but were not found by Bedford, Papp, and Parkinson (1941) in adults.

This under-development is not true of all forms of congenital heart disease. The good physique of many cases of coarctation of the aorta has been referred to by several recent writers (Perlman, 1944; Bramwell, 1947; and Newman, 1948, for example). We are unaware of any series of measurements and weights, though there can be no doubt about the good physique and sometimes athletic prowess of many patients with coarctation.

Following the visit of Blalock to Guy's Hospital in September, 1947, and his demonstrations of the surgical treatment of Fallot's tetralogy, and the successful continuation of this work by Brock (Baker, Brock, Campbell, and Suzman, 1949), large numbers of patients with congenital heart disease have been examined to select those suitable for operation. Enough of these have now been seen to allow conclusions to be drawn regarding some aspects of physical development in this condition. Difficulties in making a clinical diagnosis of the exact lesion mean that conclusions about differences between individual types of lesion are on a less sure foundation than those between congenital heart lesions as a whole and the normal.

Sex and Age Distribution

The height and weight of the first 200 cases, for which our records were complete, have been analysed. The sex and age distribution of these and the preliminary clinical diagnosis made are shown in table 1. The figures are substantially the same as for the first 340 cases. The proportions were about six boys for each five girls. The numbers in each five-year period fell, and if the numbers were plotted by years the fall was seen to be sharpest from about seven to fourteen years and then more gradual, partly because the smaller number of patients surviving after fifteen years of age have presumably less defective hearts and a longer life is possible. As regards the diagnosis, perhaps more cases should have been moved from 'Fallot's tetralogy' to the doubtful group. Many of this latter group were infants, in whom more certain diagnosis is often not possible. 'Fallot +' has been used as a convenient abbreviation in some of the tables for Fallot's tetralogy plus some physical sign that indicates an additional lesion. In eight of the cases of 'Fallot +' signs suggesting a patent ductus

TABLE 1

AGE, SEX, AND DIAGNOSIS OF 200 CASES OF CONGENITAL HEART DISEASE

	Age in years	0–4	5–9	10–14	15–35	Total
Sex	Male	43	28	27	13	111
	Female	27	27	25	10	89
	Total	70	55	52	23	200
Lesion	Fallot's tetralogy	23	27	26	11	87
	Possible Fallot	15	4	1	2	22
	*'Fallot +'	3	1	5	1	10
	Other lesions	29	23	20	9	81
	Total	70	55	52	23	200

* 'Fallot +' has been used as an abbreviation for patients who have the general picture of Fallot's tetralogy, plus some other physical sign indicating an additional lesion.

arteriosus were present in addition, and there was also coarctation of the aorta in one of these; one case had aortic incompetence, and one was thought to have congenital aortic stenosis.

The ' other lesions ' included such varied groups as tricuspid atresia with a non-functioning right ventricle, pulmonary valvular stenosis with or without a patent foramen ovale, and transposition of the aorta and pulmonary artery with a septal defect, as well as cases in which no diagnosis was made. These groups were thought to be too small for individual statistical treatment.

Height

The heights of the patients are plotted in fig. 1. The average normal curves between five and fourteen years are those for London County Council school children in 1938 (Menzies, 1939). No comparable figures for ages above and below this could be found, the lines below five years being adopted from Holt (1940) and those above fourteen years following Cruikshank (1946). Only thirty-four of these 200 children are an inch or more above this average height, whereas 124 are the same amount below it. Their average is 96·4 per cent. of average normal, or about 1 in. below normal for a child of one year, and 2¼ in. below for an adult.

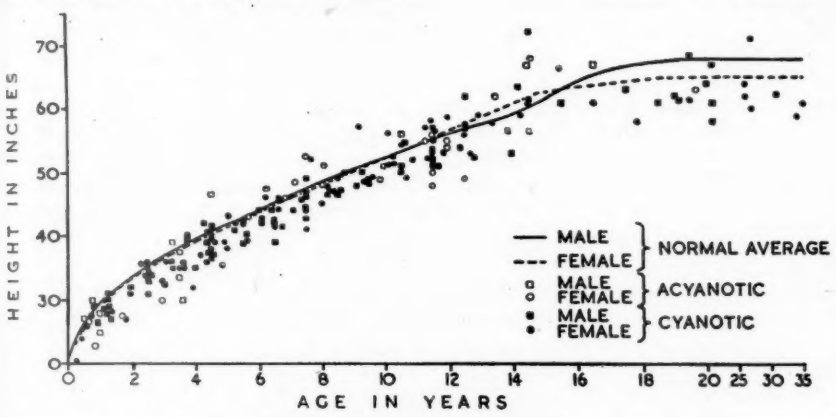

FIG. 1.—Relationship of height and age in congenital heart disease. It will be seen that most of the cyanotic cases are below the line indicating the normal average, but not greatly, the average being only 3 per cent. below.

The patients were classified by their cyanosis on the following scale.

Grade 1. Cyanosis on exertion only.
Grade 2. Cyanosis always present, but not very obvious at a glance.
Grade 3. Cyanosis moderately severe at rest and obvious at a glance.
Grade 4. Cyanosis gross at rest.

'Severe' cyanosis in this paper means those cases placed in grade 4 and between 3 and 4, and 'moderate' cyanosis, those in grades 3 and 2. It will be seen that the acyanotic group are not all strictly acyanotic, as a proportion of them, about one-quarter, were reported to have slight cyanosis on exertion or sometimes in very cold weather. We feel that in this border line group it is difficult to exclude peripheral cyanosis and for this reason, among others, such patients are better omitted from the definite cyanotic group.

TABLE 2
PERCENTAGE OF AVERAGE NORMAL HEIGHT OF 200 CASES OF CONGENITAL HEART DISEASE

Divided by lesion	Total			Divided by cyanosis
Lesion	Percentage of average normal height			Cyanosis
Fallot's tetralogy ..	97·1		94·0	Severe
Possible Fallot's and ' Fallot's +'	95·5	96·4	96·7	Moderate
Other lesions	96·0		97·8	Nil

A similar classification was made as regards disability. ' Severe ' disability means that the patient was able to walk very little and was made dyspnoeic by a short distance, such as 50 yards.

In general, the greater the degree of cyanosis the greater the effect on the growth of the patient (table 2).

The average height in the acyanotic group was nearly 98 per cent. of the normal, but in those with severe cyanosis it was only 94 per cent. For a given degree of cyanosis, however, those with Fallot's tetralogy were, on the average, not so small as those with other lesions (table 3).

Statistically the difference between the heights of those with Fallot's tetralogy and those with other cyanotic lesions is significant, being 2·86 times its standard error, that is being liable to occur by chance only once in 240 times (table 4). The differences between the two groups of severe and moderate cyanosis which make up these larger groups are also probably significant, though in the former the numbers are too small and in the latter the difference falls just below the conventional figure of twice its standard error (table 4).

Even if those cases with acyanotic lesions are included, and they accounted for nearly half of the

TABLE 3

COMPARISON BETWEEN HEIGHT OF COMPARABLY CYANOSED CASES WITH FALLOT'S TETRALOGY AND OTHER LESIONS

Lesion	Cyanosis	No. of Cases	Percentage of Average Normal Height			
Fallot's tetralogy	Severe	18	96·3	97·3	97·1	97·1
	Moderate	69				
	Nil	0			—	
Other lesions	Severe	10	91·5	95·4	94·5	96·0
	Moderate	33				
	Nil	38			97·8	

other lesions, those with Fallot's tetralogy still average nearer normal height than all the other lesions combined, though this difference is not sufficient to be statistically significant (table 4). This probably corresponds with the relatively good prognosis of Fallot's tetralogy compared with that of many other cyanotic lesions. Thus the average height of eleven cases of tricuspid atresia, a condition that clinically resembles Fallot's tetralogy closely but carries so much worse a prognosis, was only 94 per cent. of normal compared with an average height of eighty-seven cases of Fallot's tetralogy of 97 per cent.

Weight

The weights of these 200 patients are plotted in fig. 2, the curve of average normal being obtained as in fig. 1. Only one-tenth (19 out of the 200) are 2 lb. or more above this average, whereas eight-tenths (157) are this much below it. If a normal height to weight ratio were to be maintained an average weight of about 92 per cent. of average normal (varying between 90 and 94 per cent. in different age groups) would be expected for an average height of 96·4 per cent. of normal. In fact their weights average only 85 per cent. of average normal.

A large majority of these patients are more under weight than they are below normal height, and this is well shown in fig. 3 in which height is plotted against weight. The curve of average normal is plotted from the figures for average normal for males used in figs. 1 and 2. The curve for females lies so close to this that it has been omitted. As age increases in these patients weight comes to depend progressively more on age and less on height, so that only the weights of those below twenty years of age have been plotted. In this figure only 16 patients are more than 2 lb. above the normal weight for their actual height, whereas 138

TABLE 4

STATISTICAL SIGNIFICANCE OF DIFFERENCES IN HEIGHT

Cyanosis	Lesion	Percentage of normal height	Standard deviation	Standard error	Significance*
All grades	Fallot	97·1	±5·0	±0·54	2·86
	Other	94·5	±4·85	±0·74	
Severe	Fallot	96·3	±4·31	±1·08	2·31
	Other	91·5	±5·61	±1·77	
Moderate	Fallot	97·3	±5·13	±0·62	1·95
	Other	95·4	±4·31	±0·75	
Fallot's tetralogy (all cases)		97·1	±5·0	±0·54	1·13
All other cases including acyanotic ..		96·0	±7·3	±0·81	

* The difference of the means divided by the square root of the sum of the squares of the standard errors. Figures over 2 may be taken as significant.

are more than 2 lb. below it. Almost all these children were, therefore, under the average weight not only for their age but also for their height.

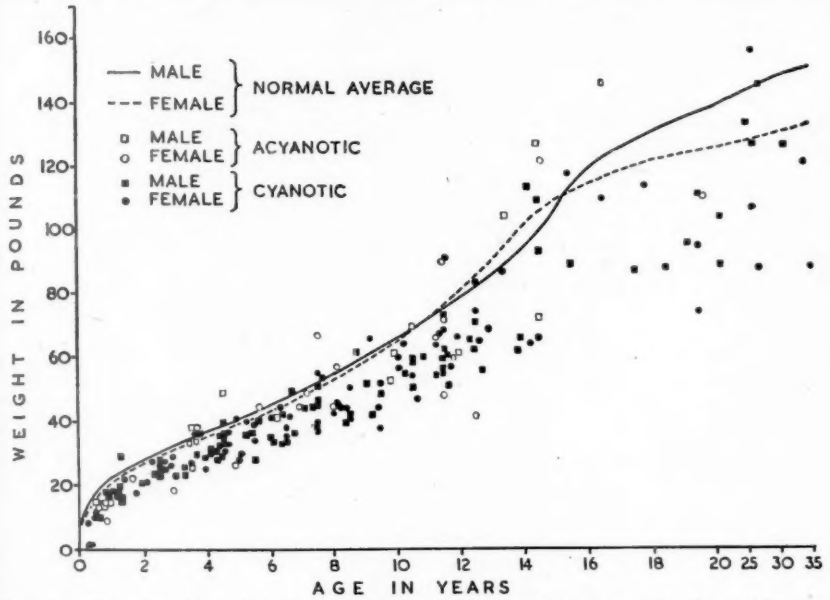

FIG. 2.—Relationship of weight and age in congenital heart disease. A few of the acyanotic cases are above weight, but this is exceptional with the cyanotic cases and many are considerably below weight, much more so than as regards height, the average deficiency being 15 per cent.

As in the case of height, there is some correspondence between the degree of cyanosis and underweight (table 5), those without cyanosis being nearly 91 per cent. and those with severe cyanosis being under 77 per cent. of average normal weight. But those with Fallot's tetralogy are less affected than those with other lesions (table 6), the relative figures for Fallot's tetralogy and for other lesions being 80 and 73 for severely cyanotic and 89 and 80 respectively for moderately cyanotic cases. The figure for thirteen cases of tricuspid atresia, not all of whom are included above, was 78. It appears, therefore, that cyanosis alone is not responsible for the under-development of these children. Another factor, as pointed out by Taussig (1947), may be a left to right shunt reducing the volume of the systemic circulation, such as occurs in patent ductus arteriosus, auricular septal defect, transposition of the great vessels, but this left to right shunt is not present in Fallot's tetralogy.

The mothers were almost unanimous in complaining about the difficulty of making their children eat. But in addition to an absence of fat, the extremely poor muscular development, made worse by the absence of any normal exercise, must add to the deficiency in weight.

TABLE 5

PERCENTAGE OF AVERAGE NORMAL WEIGHT OF 200 CASES OF CONGENITAL HEART DISEASE

Divided by lesion			Divided by cyanosis
Lesion	Percentage of average normal weight		Cyanosis
Fallot's tetralogy	87·2	76·9	Severe
Possible Fallot and 'Fallot +'	81·7	85·6	Moderate
Other lesions	84·1	90·7	Nil
	85·1		

Age of Walking

As the degree of physical development may be less than that of normal children, so may the rate of this be retarded and the milestones of infancy reached late. Thus, of a total of 294 patients, only 52 per cent. were walking by the age of eighteen months, and 73 per cent. by two years. But whereas out of forty-nine patients who were not cyanosed, 76 per cent. were walking by eighteen months and 92 per cent. by two years (figures probably not much

TABLE 6

COMPARISON BETWEEN WEIGHT OF COMPARABLY CYANOSED CASES WITH FALLOT'S TETRALOGY AND OTHER LESIONS

Lesion	Cyanosis	No. of cases	Percentage of average normal weight		
Fallot's tetralogy	Severe	18	80·3	87·2	87·2
	Moderate	69	89·0		
	Nil	0	—		
Other lesions	Severe	10	73·2	78·3	84·1
	Moderate	33	79·8		
	Nil	38	90·7		

below those for normal children) corresponding percentages for 245 cyanotic patients were only 47 and 69 per cent. respectively. Only 60 per cent.

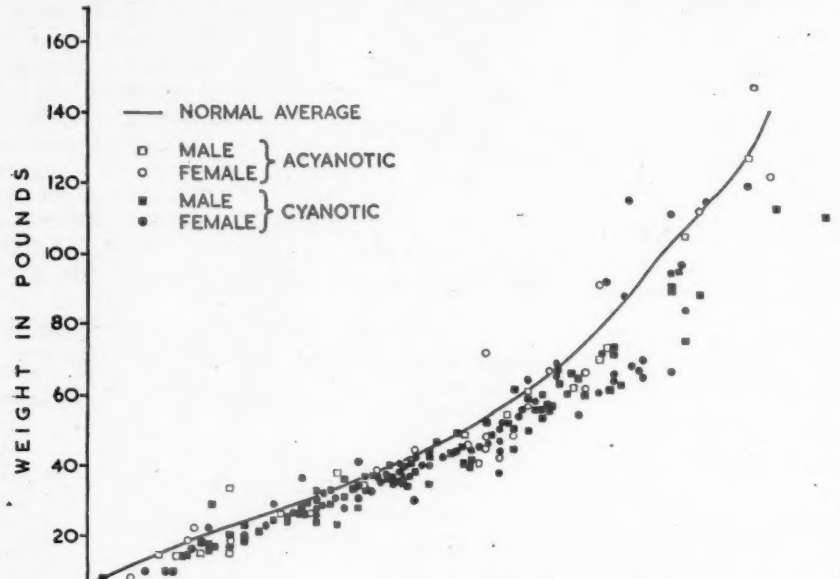

FIG. 3.—Relationship of height and weight in congenital heart disease. The normal curve is taken from the average normals of figs. 1 and 2. This shows in another form that the weight is much more reduced than the height as the result of cyanotic congenital heart disease.

of those severely cyanosed were walking by two years, and only 47 per cent. of those in whom severe cyanosis dated from birth (table 7, columns 4 and 6).

This correlation makes it reasonable to infer that cyanosis or presumably the reduction in the normal oxygen saturation of the blood is one of the factors responsible for the lateness in walking. But the poor muscular development may itself be partly responsible and these two will react on each other, the muscles failing to get the stimulus to further development that walking would normally produce.

Although we show that walking is somewhat delayed in many severely cyanotic cases, we would emphasize that great delay is unusual. Case 0015 did not walk till he was seven years old, but no one who saw him when he was nineteen and only able to walk 30 yards thought him mentally backward. His quick progress after operation (within a few months he was able to walk six miles, to join in the activities of a boy scout camp, and to get engineering work) was further evidence of this. There were few cases as delayed as this. Much backwardness should lead to a careful examination of the patients' mental condition and a search for other possible causes.

Mental Development and Age of Talking

Mental development, except in those with actual mental defect, appears on the whole to be normal. Most of the children are bright and intelligent, and the lack of schooling which their physical disability may cause is often overcome by the ready way in which they profit from instruction at home or simply from the close contact with adults which their disability makes necessary.

In assessing the rate of development, the age at which these patients talk has been noted. The definition of this admittedly rather indefinite time was left to the parents. The details are given in table 7 and a glance at the last four columns shows the main contrasts. In columns 5 and 7 dealing with talking the percentages only fall slowly, if at all, till the last line dealing with those with severe

TABLE 7

PERCENTAGE OF CASES WITH VARIOUS DEGREES OF CYANOSIS, WALKING AND TALKING AT EIGHTEEN MONTHS AND AT TWO YEARS

	Walking	Talking	Walking	Talking	Walking	Talking
			By 18 months		By 24 months	
Cyanosis	No. of Cases		Percentage		Percentage	
No cyanosis	49	50	76	74	92	84
All degrees	245	257	47	66	69	87
Severe	58	63	45	63	60	84
Moderate and severe, present at birth ..	65	70	37	61	55	86
Severe, present at birth	30	34	37	53	47	76

cyanosis that had been present from birth. Of the patients who were not cyanosed at rest, 74 per cent. were talking by the age of eighteen months, and 84 per cent. by two years, whereas of the cyanosed patients the corresponding figures were 66 and 87 per cent. Of those with more severe cyanosis a slightly smaller proportion were talking at eighteen months, but only among those in whom severe cyanosis had been present since birth were fewer talking by two years than among the acyanotic group (table 7). Thus the majority of these patients began to talk at the normal age, and in those who started late, cyanosis can only have played a minor part. Although we have no other figures to prove it, we think that most of these children were of at least average mental capacity. Good school reports and winning of scholarships provide some evidence, but in the main this opinion must rest on our own judgment of these children, of whom we have seen much and talked with and about a great deal. Considering the low arterial oxygen saturation and often the diminished blood flow as well, it is a surprising finding, and is, we think, a striking example of the importance of inheritance compared with environment (deficiency of oxygen) in the development of intelligence. Taussig (1947) also states that extreme anoxaemia does not cause mental retardation. As a striking example, we quote the case of one boy of sixteen who could not write as he was one of our most severe cases and his parents had never had the heart to make him learn. On his typewriter, however, he produced a magazine containing news and stories that he had written, and circulated it among his relatives.

We think that such association as is found between congenital heart disease and mental defect is because these two defects are sometimes produced by the same genetic causes, and that congenital heart disease does not produce any mental defect or permanent backwardness, though when severe cyanosis is present from an early age there may be some delay in talking. This has an important practical corollary in that no parent should be allowed to think that the improvement in the child's general condition that may follow operation can be followed by any improvement in its mental capacity.

Mental Deficiency and Mongolism

Mental defect was sometimes responsible for the delay in talking. Out of the first 400 cases seen, seventeen were recognized as being mentally defective, over 4 per cent. compared with 1·5 per cent. of town children and 3 per cent. of rural children generally (Burt, 1937). At least ten other children were considered to be backward. Thus poor mental development could account for the delay in talking in 7 per cent. Of these twenty-seven patients, five were acyanotic, eighteen slightly or moderately, and four severely cyanosed. This proportion is not significantly different from that of the whole series, and the absence of any correlation with cyanosis supports the view that cyanosis is not responsible for the mental deficiency.

Five of these children were thought to be mongols. Benda (1946) gives a wealth of information about most aspects of mongolism but few details about the heart condition, except that 75 per cent. of these dying in infancy and 35 per cent. of those surviving have congenital heart disease. Brown (1939) says that 16-25 per cent. of mongols are so affected but does not say how many of his patients with congenital heart disease were mongols. Auricular septal defect is common in mongols, and according to Abbot (1927) and Brown (1939) especially those defects due to a persistent ostium primum where the anterior cusp of the mitral valve is often divided into two halves. Taussig (1947) thinks that there is often persistent atrio-ventricularis communis, a large sized auricular and a variable sized ventricular septal defect, often with the leaflets of the mitral and tricuspid valves fused to form a single atrio-ventricular valve and opening. This produces little cyanosis or clubbing, but four of our five patients were cyanotic and were thought to have Fallot's tetralogy or some closely related lesion.

Ross (1939) tested the intelligence quotient of twenty-two children with congenital heart disease and found that they were below the standard of the general out-patients there, only 59 against 77 per cent. having an I.Q. over 70, and only 23 against 41 per cent. having an I.Q. of 91 or higher. These results are surprising, both as regards the large number of controls with an I.Q. under 70 and the children with congenital heart disease, especially as many of them had a patent ductus or a ventricular septal defect only. Ross concluded that the number studied was too small to exclude a chance difference, but that the children with congenital heart disease appeared to have a somewhat lower endowment as measured by the Binet-Simon tests. The absence of schooling may account for some of the difference.

These tests were carried out on very few of our children at first, only as a rule where some backwardness was suspected. Recently we have arranged for them more systematically, but from the early results we are doubtful if several of the tests used for assessing the intelligence quotient are reliable in distinguishing between the innate mental capacity and the educational standard in these children who have led such quiet lives at home and with so few outside contacts other than their parents.

We fully realize that we may have missed some of the more slightly mentally defective children and that some of the gravely affected ones may not have been brought to us either because they were already in institutions or for other reasons. We feel equally certain that most of our children were of good average intelligence and many seemed above this.

Onset of Puberty

We have no detailed figures about the onset of puberty, but think that it is frequently delayed in

those with the more severe disability and cyanosis where the patient is most under weight.

Deformity of the Chest

Some deformity of the chest was seen in more than a third of these patients, in 136 of 332 in whom the chest was mentioned. The commonest of these deformities were pigeon chest (14 per cent.), Harrison's grooves or sulcus (16 per cent.), and prominence of the ribs (14 per cent.) usually on the left side but sometimes on the right side only or on both sides. Each was present in about fifty cases, and about a quarter of them had more than one deformity (table 8).

TABLE 8

TYPES OF CHEST DEFORMITY PRESENT IN 136 OF 332 PATIENTS WITH CONGENITAL HEART DISEASE

		Severe	Moderate	Slight
Pigeon chest ..	48	9	25	14
Harrison's sulcus ..	52	5	13	34
Prominence of ribs	46	On left 33	On right 5	Both 8
Others ..	13	—	—	—

The incidence of deformity and of individual deformities in the patients with Fallot's tetralogy was very similar to that in patients with other lesions (table 9). This is rather surprising, as the former in general had not much cardiac enlargement and this is often thought to be a cause of such chest deformity. Most of them, however, had some hypertrophy of the right ventricle, and Taussig (1947) states that this developing at an early age is generally the cause of left-sided prominence of the chest.

The incidence among those with different degrees of disability and cyanosis was more variable (table 9), but the numbers are small and the variations inconsistent, making it difficult to draw any conclusions.

Prominence of the ribs, usually of the left side, was most striking in some of our cases, and that made the chest very asymmetrical. It was present twice as often in those with severe, as in those with less disability, but only slightly more in those with severe, than in those with little or no, cyanosis. This suggests that the deformity is related to the degree of disability and those with the greatest hypertrophy of the heart might be expected to be the most disabled. Right-sided prominence is less easy to explain. However, in one case dextrocardia was present and Taussig's explanation will again apply. In two others it was due to scoliosis.

Pigeon chest deformity and Harrison's sulcus seemed to show no significant correlation with disability or cyanosis so it is unlikely that these were a direct cause of the deformities.

Naish (1945) emphasized that Harrison's sulcus was found in congenital heart disease without rickets or chronic pulmonary disease. The incidence of Harrison's sulcus in our cases was much less than that found by Naish and Wallis (1948) in the congenital heart cases they examined, and indeed less than they found in normal children. Their paper is of much interest, not only for its rediscovery of Harrison's original description, but for the discussion of its mode of production. The abnormalities of the chest in our children was noted at the same time as the general examination which naturally concentrated on the heart, and minor deformities may well have been missed. But a check, where possible, on subsequent visits has shown that this was infrequent. Clearly Naish and Wallis, finding the deformity in 45 per cent. of

TABLE 9

PERCENTAGE OF CASES WITH VARIOUS CHEST DEFORMITIES, DIVIDED BY LESION, BY DISABILITY, AND BY CYANOSIS

		Percentage* of Cases with			
		Any Deformity	Pigeon chest	Harrison's sulcus	Prominence of ribs
Lesion	Fallot	37	13	12	12
	Others	36	10	12	15
Disability	Severe	40	11	5	21
	Moderate ..	40	12	15	11
	Slight or nil ..	28	15	10	10
Cyanosis	Severe	29	7	7	14
	Moderate ..	40	14	15	11
	Nil	25	9	9	11

* These figures are given as a percentage of 400, the total number of cases seen, as it is considered that at least in the majority of the 63 cases in which the chest is not mentioned, deformity was trivial or not present.

normal children, are dealing with a degree of the sulcus that is almost physiological and even their deeper groove of $\frac{1}{16}$ in. was present in nearly 7 per cent. They found Harrison's grooves in two-thirds of the patients with congenital heart disease and also refer to the marked indrawing of the lower intercostal spaces (at the same level as the sulcus) in some cases. We have noted this in an extreme form in some patients with large hearts.

Scoliosis was present in 25 of 400 cases excluding minor degrees of the condition. In four of these it was thought to be congenital and in two this was associated with hemi-vertebrae. In three cases it was extreme so that the heart was grossly displaced, and in one of these paraplegia developed from pressure on the cord (Case 0086).

Blalock (personal communication, 1947) suggested that unduly visible veins over the chest wall were common and were some indication of the extent of the collateral circulation likely to be found at operation. We have, therefore, looked for them and recorded their presence. They were seen, especially over the upper half of the front of the chest, but were often present on the scalp and face of the smaller children, and in the fingers and hands of those with severe clubbing. Sometimes the fingers have a most curious appearance, the dusky hue and dilated veins extending beyond the terminal phalanx so that at times the parents say the ends of the fingers go almost black. Occasionally the dilated veins are more generalized.

Dilated or unduly prominent veins were noted in 107 cases, and their absence in 198. Cyanosis was present in the majority of these with dilatation, and the more severe the cyanosis the greater it tended to be. Thus among the acyanotic patients only 11 per cent. showed this dilatation and it was slight in three-quarters of them; while among the less severely cyanosed patients 30 per cent. showed it and in half of them it was considerable. Among those with severe cyanosis dilatation was present in 37 per cent., and of considerable degree in more than three-quarters.

Summary

Some aspects of the physical and mental development of 400 children with congenital heart disease, mainly cyanotic, have been discussed, and 200 cases where the data were complete have been analysed more fully as regards their height and weight. Fallot's tetralogy was the diagnosis made most commonly; this, or some closely related lesion, was present in nearly half of all the cases, and in two-thirds of those who were cyanotic.

The children were, on the whole, slightly below the expected height for their age, and the average figure was 96 per cent. of the normal. This means that a child of one year was more than 1 in. below, and a young adult $2\frac{1}{4}$ in. below, the average.

The weight was much more below standard than the height so that the children looked thin, and the average figures was as low as 85 per cent. of the expected normal. Eight-tenths of them were more than 2 lb. below the average weight and only one-tenth were this amount above it.

Comparison of the height and weight showed that they were below the expected weight for their height as well as below the expected weight for their age.

Both as regards height and weight, those who had severe cyanosis were more below the expected level than those who had moderate cyanosis, and still more below those who were acyanotic. Those who were diagnosed as cases of Fallot's tetralogy were less below height and weight than the other comparably cyanotic cases.

The ages of walking and talking were taken as measures of their general development. There was some delay among the cyanotic cases and only 73 per cent. of them were walking by the age of two years. When there was severe cyanosis that dated from birth less than half (47 per cent.) were walking by the age of two years; but great delay was not found, and where children are not walking by the age of three years other causes must be looked for.

There was less delay in the age of talking, but here, too, among those who had been severely cyanosed from birth, a smaller proportion were talking by eighteen months, though by two years of age this delay had almost been overcome.

We thought that the mental capacity of these children was normal and well up to the average, though many were educationally backward. There were 4 per cent. who were defective, a larger proportion than among children in general, but, partly because of the good normal development of the others, we think this was a second associated defect rather than a direct effect of the cyanosis and anoxaemia.

Among these cases there were five mongols and four of them were cyanotic, though auricular septal defects, which do not as a rule produce cyanosis, are recognized as the commonest congenital heart defect in mongols.

Some chest deformity was present in many of these children; about 15 per cent. showed pigeon chest, 15 per cent. Harrison's sulcus, and 15 per cent. some prominence of the ribs, generally on the left side. Scoliosis was not uncommon and was occasionally severe, and this and some other deformities of posture had often been made worse by squatting.

We wish to thank Dr. P. R. Evans for his advice regarding the milestones of children's development, though he must not be held responsible for the standards we have finally adopted.

REFERENCES

Abbot, M. E. (1927). 'Osler's Modern Medicine,' **4**, 612. London.

Baker, C., Brock, R. C., Campbell, M., and Suzman, S. (1949). *Brit. Heart J.*, **11**, 170.

Bedford, D. E., Papp, C., and Parkinson, J. (1941). *Brit. Heart J.*, **3**, 37.

Benda, C. E. (1946). 'Mongolism and Cretinism.' Grune and Stratton. New York.

Benn, J. (1947). *Brit. Heart J.*, **9**, 283.

Bramwell, C. (1947). *Brit. Heart J.*, **9**, 100.

Brown, J. W. (1939). 'Congenital Heart Disease.' John Bale, Ltd. London.

Burt, C. (1937). 'Backward Child.' University of London Press.

Cruickshank, E. W. H. (1946). 'Food and Nutrition.' Livingstone. Edinburgh.

Holt, L. E., and McIntosh, R. (1940). 'Holt's Disease of Infancy and Childhood.' Appleton Century Crofts. New York.

Menzies, F. (1940). 'Report on the Average Heights and Weights of Elementary School Children in the County of London in 1938.'

Naish, A. E. (1945). *Arch. Dis. Childh.*, **20**, 185.

Naish, J., and Wallis, H. R. E. (1948). *Brit. med. J.*, **1**, 541.

Newman, M. (1948). *Brit. Heart J.*, **10**, 150.

Perlman, L. (1944). *Amer. Heart J.*, **28**, 24.

Roesler, H. (1934). *Arch. intern. Med.*, **54**, 339.

Ross, M. (1939). *J. Pediat.*, **14**, 21.

Taussig, H. B. (1947). 'Congenital Malformations of the Heart.' Commonwealth Fund. New York.

CONGENITAL TOXOPLASMOSIS: A REPORT OF TWO CASES

BY

JAMES H. HUTCHISON, O.B.E., M.D., F.R.C.P., F.R.F.P.S.G.

(From the Department of Child Health, University of Glasgow, and the Royal Hospital for Sick Children, Glasgow)

Human infection by the protozoan *Toxoplasma hominis* has been reported quite frequently in the Americas and in continental Europe. The first case proved to be due to toxoplasma was reported in the United States by Wolf, Cowen, and Paige in 1939. In retrospect four earlier cases have been accepted, although the true nature of the infection was not correctly recognized at the time of reporting (Janku, 1923; Torres, 1927; Richter, 1936; and Wolf and Cowen, 1937). The genus toxoplasma has been identified in many animals and birds (Callahan, Russell, and Smith, 1946), and as it has been found in a dog in Great Britain (Heeley, 1948), there is every possibility that the disease in humans may be less uncommon than the rarity of published cases in British medical literature suggests. In fact, it seems reasonable to suppose that an increased awareness of the existence of the disease would lead to its more frequent recognition. The first undoubted case to be described in the United Kingdom was by Jacoby and Sagorin in 1948.

After this paper had been prepared for press four more British cases have been described, two by Farquhar and Turner, (1949), one by Ridley, (1949), and one by A. B. Nutt on July 1st, 1949, at the Annual Meeting of the B.M.A. at Harrogate. Parsons (1946) and Baar (1946) described neonatal cases which resembled toxoplasmosis but as parasites were not found at necropsy a different etiology seems likely. Before reporting two additional British cases it may be helpful to review briefly the main pathological and clinical features.

Pathology

The parasite is a crescentic organism pointed at one end and rounded at the other, 4-7μ long and 2-4μ in width. In Wright and Giemsa stains the cytoplasm appears pale blue, and a dark red to purple chromatin mass is visible near the centre or at the rounded end. In tissues the parasites occur singly, or in aggregations, ' pseudocysts,' which may be surrounded by a cyst-wall.

In both the congenital and acquired human infections the parasites may invade many of the body organs, for example, the brain, for which they appear to have a predilection, the cranial nerves, lungs, myocardium, liver, kidneys, bladder, skeletal muscle, testicles, adrenals, ovaries, and thyroid. The histological changes resulting in these tissues have been described by Sabin (1941), Paige, Cowen, and Wolf (1942), Zuelzer (1944), and Callahan, Russell and Smith (1946) among others. Zuelzer (1944) summarizes the pathological changes as follows:

> ' They consisted of acute vasculitis, foci of necrosis of tissue followed by inflammatory cell infiltrations, and productive granulomatous changes. . . . The infiltrating elements were chiefly mononuclear cells and plasma cells, but eosinophils were often present. The granulomatous lesions, noted chiefly in the central nervous system, seemed to develop in response to small numbers of parasites.'

At necropsy large areas of necrosis associated with calcification and cysts may be found in the brain. Sometimes there is widespread encephalomacia (Kean and Grocott, 1948). In patients dying in the early days of life extramedullary haemopoiesis in the liver and spleen is common and is regarded by Zuelzer (1944) as related to the toxoplasma infection.

Clinical Features

Human toxoplasmosis may take five forms (' Lancet,' 1948): (1) a congenital infection, possibly transmitted via the placenta, less probably reaching the amniotic fluid from the vagina (Paige, Cowen, and Wolf, 1942; Cowen, Wolf, and Paige, 1942); (2) an acquired acute encephalitis in older children (Sabin, 1941); (3) an acute toxoplasmosis in adults with fever, pulmonary signs, and sometimes with a diffuse maculo-papular rash indistinguishable clinically from tick typhus (Pinkerton and Weinman, 1940; Pinkerton and Henderson, 1941; Syverton and Slavin, 1946); (4) a chronic encephalitis in adults (Kean and Grocott, 1945); and (5) a symptomless infection in adults out of which presumably the first type arises during intra-uterine life. Callahan (1945) detected evidence of subclinical infection in 2·7 per cent. of individuals in the St. Louis area.

The most characteristic clinical features of the

congenital type are composed of the tetrad, hydrocephalus, intracranial calcification, bilateral macular choroido-retinitis, and disturbances of nervous function.

Hydrocephalus. This seems to be an almost constant feature of congenital toxoplasmosis and it may be associated with a large head, a head of normal size, or even with microcephalus. Adams, Adams, Kabler, and Cooney (1948) demonstrated internal hydrocephalus in all of eleven patients although three had microcephalus.

Intracranial calcification. This is extremely common although it may not be obvious radiologically during the early days of life. It takes the form of curvilinear streaks of calcification in the region of the basal ganglia or optic thalamus, or of multiple rounded opacities of varying size from 1 mm. in diameter (Dyke, Wolf, Cowen, Paige and Caffey, 1942).

Choroido-retinitis. The macular region is chiefly affected and choroido-retinitis is associated with rapidly developing optic atrophy in some cases. It has to be differentiated from the changes seen in (a) pseudoglioma; (b) intra-ocular tumour; (c) traumatic lesions; (d) hereditary macular defects; (2) congenital developmental defects of the choroid and retina (Callahan, Russell, and Smith, 1946). In one of Zuelzer's (1944) cases the typical appearances did not develop until the infant was five months of age.

Disturbances of nervous function. Such disturbances as mental deficiency, spasticity, optic atrophy, and convulsions are frequently but not necessarily present. Cowen, Wolf, and Paige (1942) suggest that the mental deficiency is usually mild in degree. One of the patients described by Adams, Adams, Kabler, and Cooney (1948) had a better than average intelligence in spite of marked hydrocephalus. Crothers (1943) and Adams, Horns, and Eklund (1946) have described patients in whom the intelligence was not affected; the latter authors' patient had also marked hydrocephalus which was cured by ablation of the right choroid plexus.

Various other less frequently reported features may be encountered. Neonatal jaundice with enlargement of liver and spleen and with erythroblastaemia may simulate haemolytic disease (Zuelzer, 1944; Callahan, Russell, and Smith, 1946). Ocular signs other than choroido-retinitis which have been reported are coloboma of the macula (Janku, 1923), microphthalmos, enophthalmos, ocular palsies, nystagmus, and papilloedema (Paige, Cowen, and Wolf, 1942; Callahan, Russell, and Smith, 1946). Susceptibility to respiratory infections may be related to the toxoplasmic pneumonitis frequently found at necropsy. Diarrhoea and vomiting usher in the disease in some infants. Myocarditis has frequently been reported, usually without obvious clinical evidence of its presence, although one infant described by Cowen, Wolf, and Paige (1942) had oedema. A curiously unstable temperature and a diffuse maculo-papular rash in the neonatal period were also described by Cowen, Wolf, and Paige (1942). The cerebrospinal fluid in many of the cases reported has been xanthochromic with pleocytosis and a high protein content (Paige, Cowen, and Wolf, 1942; Zuelzer, 1944; Adams, Adams, Kabler, and Cooney, 1948). Rarely toxoplasma has been found in smears (Wolf and Cowen, 1937; Cowen, Wolf, and Paige, 1942).

Diagnosis

The only certain proof of toxoplasmosis is the recovery of the toxoplasma from the body fluids, especially from the cerebrospinal fluid, by intracerebral and intraperitoneal inoculation of rabbits or mice. This is, however, often unsuccessful even when carried out soon after birth (Zuelzer, 1944; Miller, 1947); and, of course, in older patients the infection may have subsided leaving only the permanent residua.

A test for the demonstration of toxoplasma-neutralizing antibodies in the serum of affected persons has been described in detail by Sabin and Ruchman (1942), Sabin (1942), Cowen, Wolf, and Paige (1942), and Callahan (1945). A positive test in the mother or infant is strong presumptive evidence of toxoplasmosis but a negative result does not at all rule out the possibility of its having been present and subsided (Sabin, 1941; Crothers, 1943; Schwartzmann, Maffia, Crusius, and Brunhoffer, 1948). A more satisfactory test, the cytoplasm-modifying antibody test, has recently been described by Sabin and Feldman (1948); this has been found more useful than the neutralization test because of its simplicity and because the quantitative data obtained permits differentiation between very old and more recent infection.

Prognosis

The almost invariably fatal outcome in the early reports of cases of congenital toxoplasmosis at first gave the impression that this was a progressive disease. It is, however, now obvious that in some patients with manifest signs of the disease the infection may cause only limited disability or die out altogether. Sabin (1942) found positive neutralizing toxoplasma antibody tests in nine out of ten individuals suffering only from choroido-retinitis of unknown cause. Johnson, Fried, Broaddus, and Lamfrom (1946) obtained positive antibody tests in twenty patients with choroido-retinitis in only four of whom was other evidence (intracranial calcification) of toxoplasmosis present. They also describe the interesting case of a woman aged twenty-two years with a positive antibody test in whom a quiescent chorioretinal lesion became activated during each of three pregnancies. The only living child (of the second pregnancy) seemed normal, and the foetus obtained from the third pregnancy by therapeutic abortion showed no evidence of toxoplasmic infection. They further report that two of their four laboratory workers

acquired subclinical toxoplasmosis and that one of these later gave birth to a perfectly normal child. On the other hand, Sabin (1942) obtained positive antibody tests in three out of four mothers who had given birth to stillborn hydrocephalic or microcephalic babies, and also in three out of eight mothers who had given birth to anencephalic monsters.

It would appear, then, that a woman with subclinical toxoplasmosis may produce a foetus so diseased as to be incapable of extra-uterine life, or an infant with manifest congenital toxoplasmosis, or an unaffected normal infant. Furthermore, the infected infant may be either severely disabled or suffer only moderate disability compatible with a useful existence.

Case Reports

Case 1. P.N., a girl aged a year and three months, was admitted to the Royal Hospital for Sick Children, Glasgow, on December 2, 1948, with pneumococcal broncho-pneumonia which quickly recovered on penicillin and sulphamerazine.

She had been a full-time baby weighing 6 lb. 2 oz. at birth. She was breast-fed for six months and gained weight at a normal rate. She sat up unsupported at eight months, started to say a few words at fifteen months, but was not yet walking when she contracted pneumonia.

The mother noted that she had an internal squint of both eyes at birth, and thought that as early as eight weeks the infant failed to see properly in comparison with her previous children at the same age. On July 3, 1948, when she was thirteen months old she was for the first time examined at the Glasgow Eye Infirmary. There was at that time 'a marked disseminated pigmentary choroido-retinitis affecting the maculae' of both eyes. The Wassermann reaction was negative. On July 13, 1948, repeat fundal examination revealed, in addition, a coloboma of the right disc and choroid.

The mother was aged thirty-two years and was healthy. The father was aged thirty-seven years; for some years he had been addicted to drugs and, in fact, he died from an overdose of self-administered chloroform while his child was in the hospital. There are three older children, a boy aged five years, and twin girls aged three years, all of whom are healthy.

On examination after admission the child was seen to be thin, 86 per cent. of the expected weight for her age. The head circumference was 17¾ in. (average normal 18½ in.). On admission she was profoundly ill, dyspnoeic and cyanotic, although her rectal temperature never rose above 100° F. The signs of broncho-pneumonia were present throughout both lungs. There was no evidence of cardio-vascular, gastro-intestinal or renal disease.

When she had recovered from the pneumonia it was obvious that she was a high-grade mental defective. There was no spasticity but the knee and ankle-jerks were exaggerated and the plantar responses were extensor. Her vision was obviously poor and there was a bilateral internal strabismus.

Ophthalmoscopy showed pale discs and narrowed arteries. There was fine pigmentation over the whole of both fundi, and there were atrophic white areas at both maculae with marked surrounding pigmentation. A proliferative pigmented mass obscured the right choroidal coloboma. The appearances were those of bilateral choroido-retinitis.

The following laboratory investigations were carried out:

The Mantoux test (1/5,000) was negative. A blood count showed haemoglobin 11 g. per cent.; red cells 3·95 million per c.mm.; white cells 12,800 per c.mm.

A laryngeal swab produced a heavy growth of pneumococci and scanty coliform organisms on culture.

X-ray examination of the chest showed patchy consolidation of both lungs, and of the skull several areas of calcification in the form of linear streaks in the region of the optic thalamus which were too fine for photographic reproduction.

Examination of the cerebrospinal fluid gave a normal pressure. The Pandy reaction was positive: cells 4 per c.mm.; protein 36 mg. per cent.; chlorides 719 mg. per cent.

The Wassermann reaction was negative.

Several mice and guinea-pigs were inoculated intracerebrally and intraperitoneally both in the Royal Hospital for Sick Children and in the Bacteriological Department of Sheffield University, but none of the animals developed clinical or post-mortem evidence of toxoplasmosis.

A pneumo-encephalogram showed a severe cortical defect of the left cerebral hemisphere. The ventricular system failed to fill with air.

The sera from the patient (P.N.) and her mother (Mrs. N.) were sent to Dr. Sven Gard, of the Statens Bakteriologiska Laboratorium, Stockholm, for the cytoplasm-modifying antibody test of Sabin and Feldman (1948). Both specimens yielded positive results with titres of 1:100 (final dilution 1:200). Dr. Sven Gard, who had used this test on about 300 sera, regarded the results as highly significant and indicative of toxoplasmosis. As the titre usually exceeds 1:200 during the active phase of the infection it is assumed that the process in the child as well as in the mother has subsided.

Professor C. P. Beattie, of the Bacteriology Department, Sheffield University, obtained the following results from a toxoplasma neutralizing antibody test on the sera of P.N. and Mrs. N.:

The sera of P.N. in the first test neutralized 10 to 100 skin doses, and in the second 100 to 1,000 skin doses. That of Mrs. N. neutralized 10 to 100 skin doses.

Serum inoculations intracerebrally and intraperitoneally into mice failed to produce toxoplasma infection.

The mother and three older children were all examined and appeared to be healthy. None

showed the presence of choroido-retinitis or intracranial calcification. The neutralizing antibody tests on the three children were negative (Professor C. P. Beattie).

The patient has been seen as an out-patient on several occasions since discharge from hospital on February 26, 1949. She is in good general health and has not had any recurrence of chest infection.

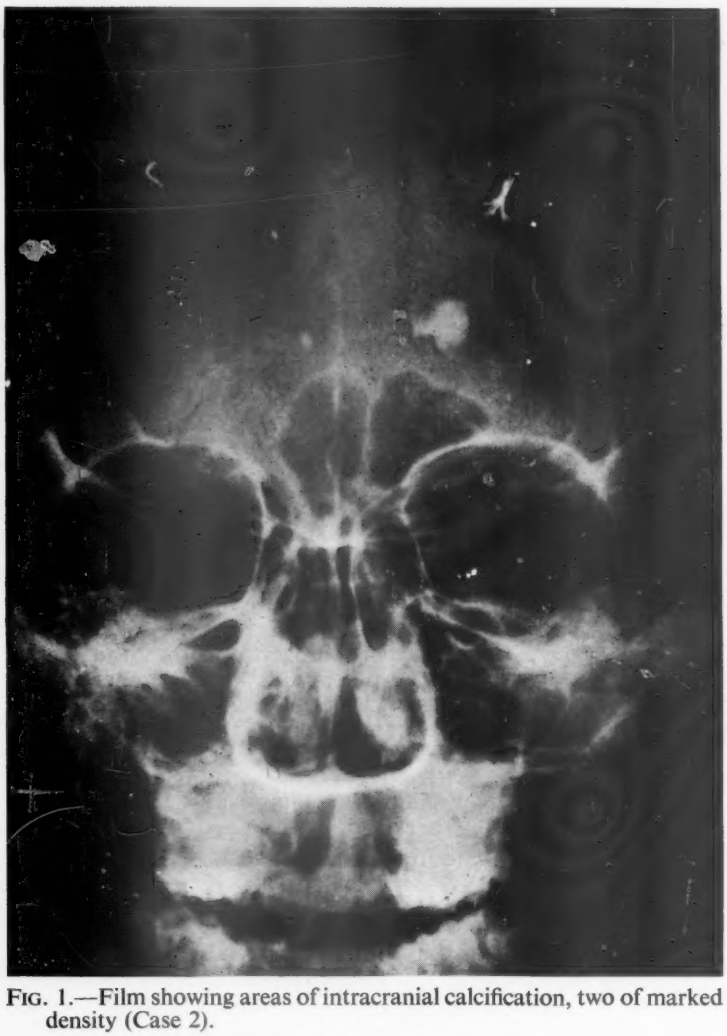

FIG. 1.—Film showing areas of intracranial calcification, two of marked density (Case 2).

Case 2. J.W., a boy aged sixteen years, reported to the out-patient department of Glasgow Eye Infirmary on February 12, 1949, complaining of weakness of vision of long standing.

The history obtained later from his mother was as follows. He was her first child, a full-term healthy baby weighing 7 lb. He developed normally, walking at eleven months and talking at twelve months. At the age of six months, however, it was noted that he failed to grasp objects which were near his face. At the age of four years he was examined by an ophthalmologist who reported that the boy had some retinal abnormality in both eyes and prescribed glasses which were worn thereafter. He left school at the age of fifteen years and works as a general labourer.

The mother was aged forty-one years and the patient's father, who is not the mother's husband, was aged forty-one years. Both are healthy. The mother has since had two healthy children by her husband.

On examination the boy appeared to be a healthy, well-developed youth of low average intelligence. Clinically there was no evidence of organic disease other than in the eyes. (Visual acuity: right eye 6/60; left eye 6/60.) There was limited lateral and upward movement of the eyes and an occasional nystagmoid jerk was seen.

Ophthalmoscopy revealed old, inactive, extensive bilateral choroido-retinitis especially affecting the maculae.

A radiograph of the skull showed several patches of intracranial calcification, two being of large size and marked density (figs. 1 and 2).

The Wassermann reaction was negative.

The sera from the patient and his mother were sent to Dr. Sven Gard for the cytoplasm-modifying test. He reported the presence of toxoplasma antibody in very low concentrations in both specimens, and gave it as his opinion that as the infection in the patient presumably dated sixteen years back the results were compatible with a diagnosis of toxoplasmosis. At the same time he pointed out that similar results are given by 30 per cent. of normal adults with no history to suggest toxoplasmosis.

Professor C. P. Beattie obtained the following results from the toxoplasma neutralizing antibody test on the sera of the patient and his mother (Mrs. W.):

The sera of J.W. neutralized 10 rabbit skin test doses, but that of Mrs. W. showed no neutralization of toxoplasma.

Discussion

In case 1 the diagnosis of congenital toxoplasmosis can hardly be in doubt. There was bilateral choroido-retinitis, intracranial calcification, mental deficiency, evidence of pyramidal tract damage, and both the patient and her mother had toxoplasma antibodies in their sera in amounts not to be found in healthy people. The failure to recover toxoplasma by intracerebral and intraperitoneal inoculation of animals with the patient's serum and cerebrospinal fluid in no way precludes the diagnosis,

and seems, in fact, to be the rule rather than the exception (Miller, 1947; Adams, Adams, Kabler, and Cooney, 1948; Jacoby and Sagorin, 1948). As regards prognosis, there would seem to be no reason why this patient should not survive into adult life although obviously her brain must remain seriously damaged. Death, if it should come earlier, would probably be by way of respiratory infection to which sufferers from toxoplasmosis appear to be especially susceptible (Callahan, Russell, and Smith, 1946).

In case 2 the diagnosis of toxoplasmosis is open to doubt. The presence of toxoplasma antibodies in very low concentrations, although compatible with a diagnosis of toxoplasmosis, is not helpful because many supposedly normal people give similar results. None the less, the toxoplasmic infection in this patient was of sixteen years' duration, because symptoms were noted during the first year of life, and a high concentration of antibodies would hardly be present at the time of examination. Sabin (1941), Syverton and Slavin (1946), and others have found that antibodies may disappear within six to ten weeks after infection by toxoplasma. Levin and Moore (1942) describe an infant with the typical clinical features of congenital toxoplasmosis in whom at the age of one year the neutralizing antibody test was negative although Sabin found the complement fixation test to be positive. Heidelman (1945) obtained positive antibody tests in 63 per cent. of cases of congenital choroido-retinitis in which toxoplasma might reasonably have been suspected as the causal agent, and of nine patients with congenital choroido-retinitis and other evidence of toxoplasmosis, only five had antibodies in their sera. Heidelman states:

'Therefore it would appear that the demonstration of the neutralizing antibody should be considered a factor of moderate diagnostic value only in patients with congenital chorio-retinitis.'

Furthermore, Crothers (1943) states:

'It has been my experience that the suggestion of toxoplasmosis should arise when the ophthalmologist is puzzled by the presence of chorio-retinitis. If calcification of the brain occurs in addition the presumption is strong.'

The fact that the second patient was in good general health apart from inactive choroido-retinitis and intracranial calcification only provides further evidence to support the view of several workers (Sabin, 1942; Crothers, 1943; Callahan, 1945; Heidelman, 1945; Johnson, Fried, Broaddus and Lamfrom, 1946; Plaut, 1946; Adams, Adams, Kabler, and Cooney, 1948) that a patient may survive infection without serious disability even when the brain and eyes are involved, and that only one or two of the cardinal manifestations of the disease may be present.

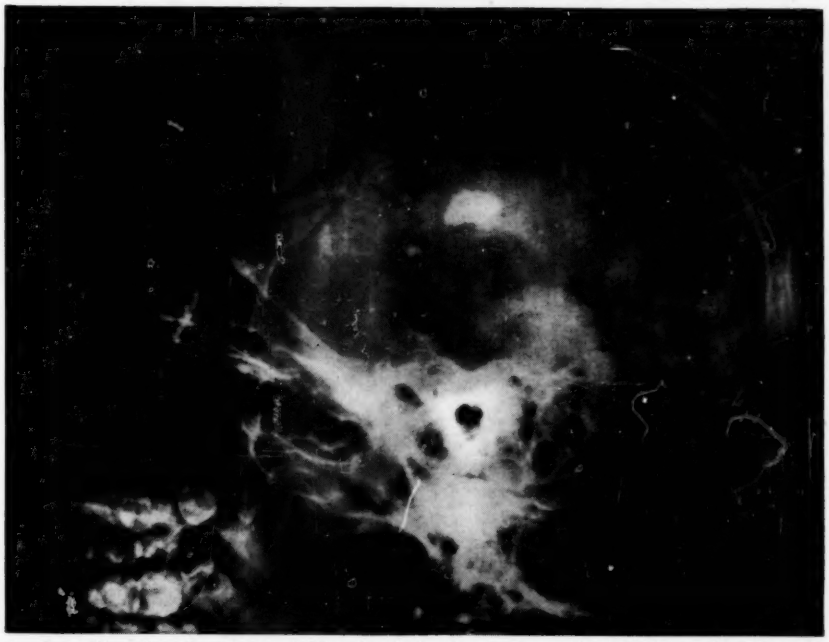

FIG. 2.—Film showing that calcification is in the region of the basal ganglia (Case 2).

I understand that in ophthalmological practice in Great Britain bilateral choroido-retinitis is not an extremely rare condition, and that when cases due to syphilis and tuberculosis are excluded there remains a number for which no cause can be found. It seems probable that if facilities for the performance of toxoplasma antibody tests were more generally available toxoplasmosis in this country would be shown to be not very uncommon. Affected patients are most likely to reach either the paediatrician, because of visual defects, mental abnormalities, abnormal heads, or as gravely ill newborn infants, or the ophthalmologist with choroido-retinitis.

Summary

The etiology, pathology, clinical and serological diagnosis, and prognosis of congenital toxoplasmosis are briefly reviewed.

Two probable cases occurring in the United Kingdom and not noted in the literature are described and discussed.

Thanks are due to Dr. J. Pendleton White, visiting surgeon, Glasgow Eye Infirmary, for permission to report case 2, and to Dr. Sven Gard,

of Stockholm, and Professor C. P. Beattie, of Sheffield for carrying out the toxoplasma antibody tests.

References

Adams, F. H., Adams, J. M., Kabler, P., and Cooney, M. (1948). *Paediatria*, **2,** 511.

——, Horns, R., and Eklund, C. (1946). *J. Pediat.*, **28,** 165.

Baar, H. S. (1946). *Brit. med. Bull.*, **4,** 178.

Callahan, W. P. (1945). *Proc. Soc. exper. Biol. Med.*, **59,** 68.

——, Russell, W. O., and Smith, M. G. (1946). *Medicine*, **25,** 343.

Cowen, D., Wolf, A., and Paige, B. H. (1942). *Arch. Neurol. Psychiat.*, **48,** 689.

Crothers, B. (1943). *Arch. Neurol. Psychiat.*, **49,** 315.

Dyke, C. G., Wolf, A., Cowen, D., Paige, B. H., and Caffey, J. (1942). *Amer. J. Roentgenol.*, **47,** 830.

Farquhar, H. G., and Turner, W.M.L. (1949). *Arch. Dis. Childh.*, **24,** 137.

Heeley, D. M. (1948). Quoted by Jacoby and Sagorin.

Heidelman, J. M. (1945). *Arch. Ophthl.*, **34,** 28.

Jacoby, N. M., and Sagorin, L. (1948). *Lancet*, **2,** 926.

Janku, J. (1923). *Čas. Lék. Čes.*, **62,** 1021.

Johnson, L. V., Fried, N., Broaddus, C. C., and Lamfrom, H. (1946). *Arch. Ophthl.*, **36,** 677.

Kean, B. H., and Grocott, R. G. (1945). *Amer. J. Path.*, **21,** 467.

—— —— (1948). *J. Amer. med. Ass.*, **136,** 104.

Lancet (1948). *Leading Article*, **2,** 934.

Levin, P. M., and Moore, H. (1942). *J. Pediat.*, **21,** 673.

Miller, M. C. (1947). *J. Pediat.*, **30,** 201.

Nutt, A. B. (1949). *Brit. med. J.*, **2,** 174.

Paige, B. H., Cowen, D., and Wolf, A. (1942). *Amer. J. Dis. Child.*, **63,** 474.

Parsons, Sir L. G. (1946). *J. Obstet. Gynec.*, **53,** 1.

Pinkerton, H., and Henderson, R. G. (1941). *J. Amer. med. Ass.*, **116,** 807.

——, and Weinman, D. (1940). *Arch. Path.*, **30,** 374.

Plaut, A. (1946). *Amer. J. Path.*, **22,** 427.

Richter, R. (1936). *Arch. Neurol. Psychiat.*, **36,** 1085.

Ridley, H. (1949). *Brit. J. Ophthal.*, **33,** 397.

Sabin, A. B. (1941). *Journ. Amer. med. Ass.*, **116,** 801.

—— (1942). *Proc. Soc. exp. Biol.*, **51,** 6.

——, and Feldman, H. A. (1948). *Science*, **108,** 660.

——, and Ruchman, I. (1942). *Proc. Soc. exp. Biol.*, **51,** 1.

Schwartzman, J., Maffia, A., Crusius, M. E., and Brunhoffer, A. (1948). *J. Pediat.*, **33,** 66.

Syverton, J. T., and Slavin, H. B. (1946). *Journ. Amer. med. Ass.*, **131,** 957.

Torres, C. M. (1927). *R. Soc. Biol., Paris*, **97,** 1778.

Wolf, A., and Cowen, D. (1937). *Bull. neurol. Inst. N. Y.*, **6,** 306.

——, ——, and Paige, B. H. (1939). *Amer. J. Path.* **15,** 657.

Zuelzer, W. W. (1944). *Arch. Path.*, **38,** 1.

COMPLETE AURICULO-VENTRICULAR HEART BLOCK IN THE FOETUS AND NEWBORN

BY

I. D. RILEY, M.D., M.R.C.P., D.C.H.

(Department of Paediatrics and Child Health, University of Leeds)

It has been known for many years that abnormalities are sometimes detectable in the foetal pulse, and that their recognition before or during labour has led to an erroneous diagnosis of foetal distress. The use of the electrocardiograph and the phonocardiograph has shown that several kinds of abnormality may occur, and that there is much difference between them in prognosis.

Case Reports

Case 1. R.T. was born on July 29, 1947, of healthy parents. On July 18, 1947, antenatal examination showed that the foetal heart was slow and irregular. A murmur was audible and it was thought to be a 'funic souffle.' The irregular pulse was interpreted as evidence of foetal distress, and on July 26, 1947, the membranes were punctured to induce labour.

The child was born three days later after a normal labour. The foetal pulse remained at 80 throughout labour. At birth the baby appeared to be normal; there was no cyanosis and feeds were taken well, but examination of the heart showed a rate constantly below 60. The beat was regular. No murmur was audible in the praecordium, but the first heart sound to the left of the sternum was blurred and indistinct, in comparison with the clear-cut second sound.

The child was sent home, but was brought in again on Dec. 18, 1947. Up to this time his progress and gain in weight had been satisfactory. The slow pulse rate persisted. An electrocardiogram at this time showed a complete auriculo-ventricular block.

The child was next seen when six months old in January, 1948, when he was admitted to hospital because of a severe attack of bronchitis. His history in the meantime was that he had gained weight satisfactorily until he was three months old and 12 lb. in weight, at which time the breast milk failed and he was put on artificial feeding. From this time onwards he was difficult to feed, and only weighed 11 lb. 4 oz. on admission. Other evidences of nutritional failure were his small size (height 23½ in., head 16¼ in., fontanelle 1 finger's breadth) and a deformity of the thorax, consisting of an indrawing of the lower costal margin on both sides.

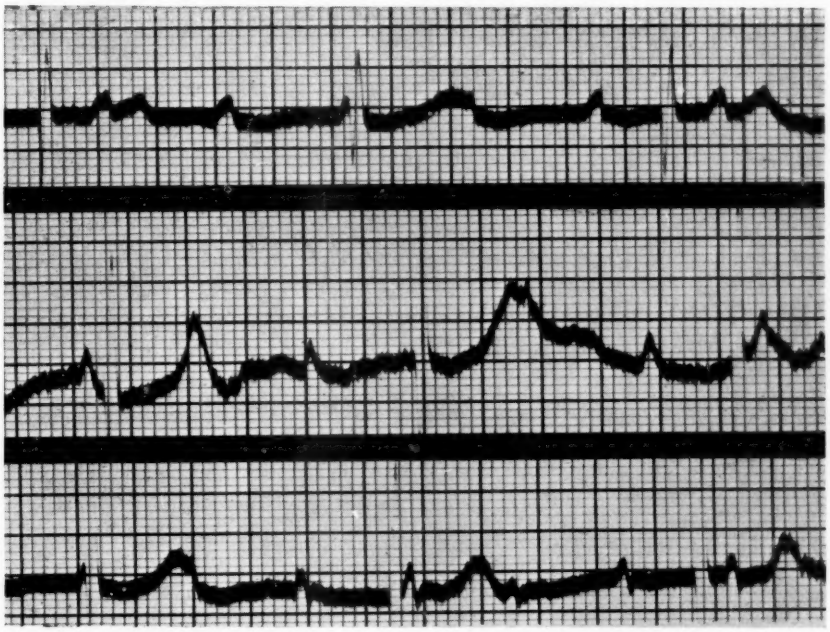

FIG. 1—Electrocardiogram showing complete heart block (Case 1.)

There was now a loud, rasping, systolic murmur, maximal in the third left space, close to the sternum and propagated outwards and upwards. This murmur replaced the first sound. X-ray examination showed the heart to be much enlarged. There was no clinical evidence of any pulmonary lesion more serious than bronchitis. The heart rate

remained steady, and the cyanosis which was present was attributed to the cardiac condition rather than to the bronchitis.

The only untoward incident during the course of the illness was an attack of vomiting followed by cyanosis and collapse lasting half an hour.

The child developed chickenpox while in the ward and his pulse rate rose to 120 for eleven days and then suddenly fell to 60.

His recovery from the bronchitis was good and it was felt that the infectious process had embarrassed the heart less than might have been expected.

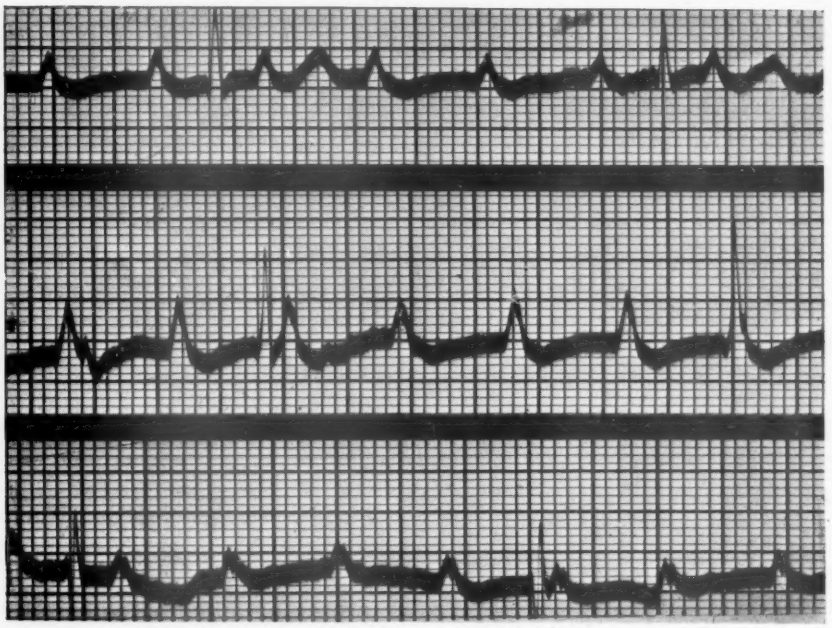

FIG. 2.—Electrocardiogram showing complete heart block (Case 2.)

While in the ward he frequently refused his feeds, a common occurrence in congenital heart disease.

Case 2. R.P. was first seen on Aug. 19, 1946, when three weeks old. His birthweight had been 6 lb. 10 oz. He was a first child and was brought to hospital because his mother noticed that he was blue immediately after birth. The blueness continued to appear on crying.

On examination, inspection showed no obvious abnormality, and the infant was not cyanosed when first seen. There was, however, a loud systolic bruit all over the praecordium. The site of maximal intensity was difficult to define. The pulse was irregularly irregular and the rate was 96. An electrocardiogram showed a complete auriculo-ventricular block.

Later enquiries revealed that the child had died when eleven weeks old, and that no necropsy had been performed. No details as to the mode of death were obtainable.

Discussion

An electrocardiogram showed the presence of a complete auriculo-ventricular block in the neonatal period in both these cases. Signs were present before birth in the first case, although they were not correctly interpreted.

Communications on the subject may be considered under three headings: (1) Congenital heart block; (2) antenatal diagnosis of congenital heart block; and (3) antenatal studies with electrocardiograms and phonocardiograms.

Congenital heart block. Yater (1929) has studied this subject extensively, and he reviews the literature up to 1929, and with Lyon and McNabb in a later paper (1933), up to 1933. He gives certain criteria to be used in the diagnosis, namely bradycardia early in life, a graphic record, and the absence of rheumatic fever or syphilis. Additional evidence is provided by syncope early in life, and by associated congenital heart disease. He found one case in which the irregularity was noted before birth.

Antenatal diagnosis of auricular-ventricular block. This has been made on several occasions. Sankey (1948) reviews the literature up to 1948 and gives a table of eight cases. Ottow (1939) and Heubner (1939) both insist that such a diagnosis can only be presumptive and that no prognosis can be given until some months after birth. This is borne out by Heubner's case in which the change from auriculo-ventricular block to normal rhythm occurred gradually after birth. It is of interest in this connexion to notice Sheridan and Parker's (1947) case, in which a child who had no heart block at birth, developed one during the neonatal period (Witt, 1934; Geiger and Hines, 1940; Thompson, 1943; Sjöquist, 1942; Hammond et al., 1944).

Phonographic and electrocardiogram studies. These have shown that many different disorders of the foetal pulse rate and rhythm may occur. Hyman (1930) by this method found that 9·2 per cent. of foetal hearts showed an irregularity, but Sampson (1925) found only one in thirty-three cases. Various authors have described irregularities detected by these and other methods. Sino-auricular block, paroxysmal tachycardia, flutter, and extrasystoles have all been observed (Kriszt, 1937; Frisell, 1947; Roberts, 1938; Dippel, 1934; Weinzierl, 1927).

Prognosis. The presence of complete auriculo-ventricular block combined with other evidence of congenital heart disease has been associated with short duration of life in the cases so far reported. This makes its accurate diagnosis a matter of importance. There is general agreement that the importance of all congenital anomalies of the heart beat lies in their prognostic significance, and this is very difficult to assess. It is advisable not to give a final opinion until the child is several months old and an electrocardiogram is available.

I wish to thank Professor W. S. Craig for his help in the preparation of this paper.

References

Dippel, A. L. (1934). *Amer. J. Obstet. and Gynec.*, **27,** 120.
Frisell, E. (1947). *Act. Paediatr.*, **34,** 30.
Geiger, C. J., Hines, L. E. (1940). *J. Amer. med. Ass.*, **115,** 2272.
Hammond, J. W., Stone, D. C., and Hyams, L. L. (1944). *Arch. Pediat.*, **61,** 1.
Heubner, W. (1938). *Z. Kreisl. Forsch.*, **30,** 600.
Hyman, A. S. (1930). *Amer. J. Obstet. and Gynec.*, **20,** 332.
Kriszt, J. (1937). *Orvosi Hetil*, **81,** 967.
Ottow, B. (1939). *Zbl. Gynak.*, **715,** 63.
Plant, R. K., and Steven, R. A. (1945). *Amer. Heart J.*, **30,** 615.
Rihl, J., and Weinzierl, E. (1927). *Arch. Gynak.*, **130,** 626.
Roberts, J. T. (1938). *J. Tech. Methods*, **18,** 101.
Sampson, J. J., McCalla, R. L., and Kerr, W. J. (1925-6). *Am. Heart J.*, **1,** 717.
Sankey, A. O. (1948). *Brit. med. J.*, **2,** 676.
Sheridan, V. E., and Parker, R. L. (1947). *Amer. J. Dis. Child.*, **73,** 199.
Sjöquist, I. (1896-1942). *Svenska läk tidning*, **39,** 1896. Abstract, p. 221, *Amer. J. Dis. Child.*, **73,** 1947.
Thomson, J. (1943). *Arch. Dis. Childh.*, **18,** 190.
Witt, D. B. (1934). *Amer. J. Dis. Child.*, **47,** 380.
Yater, W. M. (1929). *Amer. J. Dis. Child.*, **38,** 112.
——, Lyon, J. A., and McNabb, P. E. (1933). *J. Amer. med. Ass.*, **100,** 1831.

CASE REPORT

EMBRYOMA OF THE KIDNEY WITH SYMPTOMS AT BIRTH

BY

CYRIL JOSEPHS, M.B., B.S., D.C.H.

(From Staincliffe General Hospital, Dewsbury)

A case of embryoma of the kidney causing symptoms at birth seems to be rare enough to merit reporting.

Many names have been applied to the embryonic renal tumour, including 'Wilm's tumour,' 'mixed tumour,' 'nephroblastoma,' 'adenosarcoma.' This variety of names does not signify that they are different kinds of tumours, but merely that they vary considerably in their structure and thus different views are held regarding their histogenesis.

Willis in his book 'The Pathology of Tumours' says:

'It is now clear that there is but one entity, embryonic renal tumour appropriately called also "nephroblastoma" since it arises from and consists of immature renal blastema.'

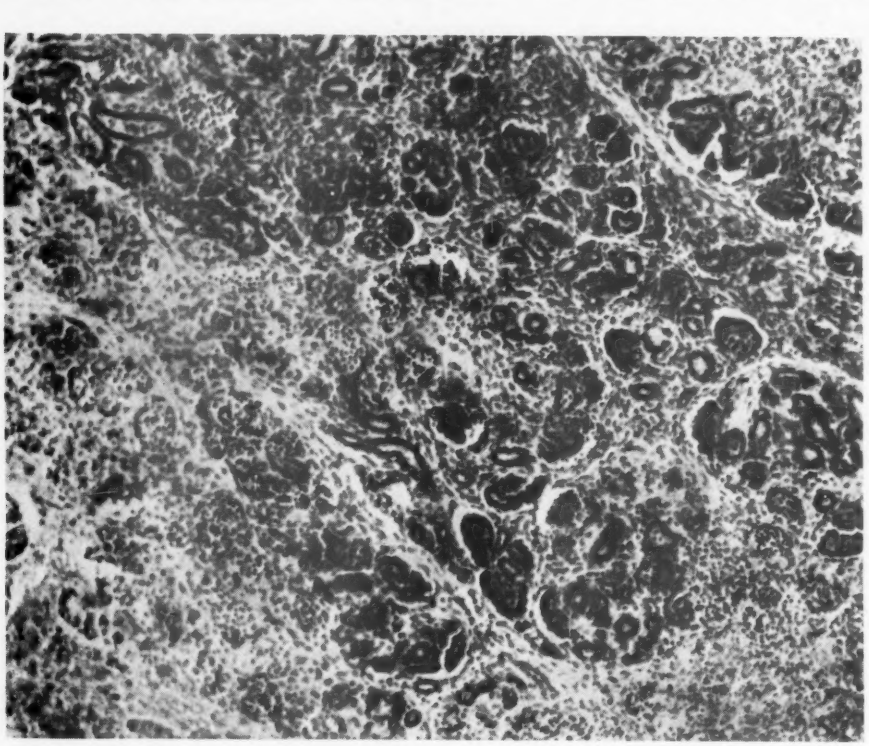

FIG. 1.—Photomicrograph of embryoma showing well differentiated connective tissue and tubules. ×98.

Symptoms from these tumours usually arise within the first three years of life and rarely after the age of ten. Although renal tumours have been found in foetuses, it is rarely that the tumour is large and able to cause symptoms at birth. Their occurrence is about twice as common in males as in females. The tumours are usually single and unilateral, but multiple or bilateral growths have been reported.

Structure. There is a great structural variety, but usually embryonic renal tissue showing different degrees of differentiation predominates.

Growth and treatment. In a small proportion of cases the tumour is confined to the kidney when first diagnosed and in these cases nephrectomy is said to be curative. Attention is drawn to the condition because of an abdominal swelling or haematuria. Even large tumours with haematuria may be curable by early surgery. However, the tumour tends to be highly malignant and metastases frequently occur in the lungs, and more rarely in liver, bones or elsewhere.

Silver has recently reported a series of eighteen cases of embryoma of the kidney. The youngest patient was three days old. In this case the signs

and symptoms appear to have been similar to those of the case reported below.

Case Report

A male baby was admitted to the hospital one hour after birth. He was full term and weighed $6\frac{1}{4}$ lb. Gross abdominal enlargement was present at birth and for this reason the midwife had had difficulty in delivering the baby. He was said to be bleeding from his penis at birth.

Examination. The baby was jaundiced. The abdomen was distended and tense and there was a firm swelling in the left flank which was dull to percussion. Blood was seen at the urethral orifice which otherwise seemed normal.

A blood count showed the haemoglobin to be 9·9 g. per 100 ml.

Examination of the urine showed large numbers of red cells and an occasional cast.

A radiograph of the abdomen confirmed the presence of a large swelling in the left flank.

A blood transfusion followed by a laparotomy and probably nephrectomy was contemplated, but unfortunately the baby died shortly after admission.

At necropsy the left kidney was found to be replaced by a cystic swelling about the size of a large grapefruit. The left suprarenal was larger than the right and was on top of the tumour and easily detached from it. Section of the tumour showed only a small rim of apparently normal kidney substance, the rest of the mass consisting of neoplasm and blood clot. No metastases were found elsewhere in the body.

Microscopical examination of the tumour showed cellular tissue differentiating into glomeruli, tubules, and non-epithelial tissue, and there were numerous areas of necrosis.

Summary

A case of embryoma of the left kidney which was present at birth is reported. The symptoms were an abdominal mass and haematuria.

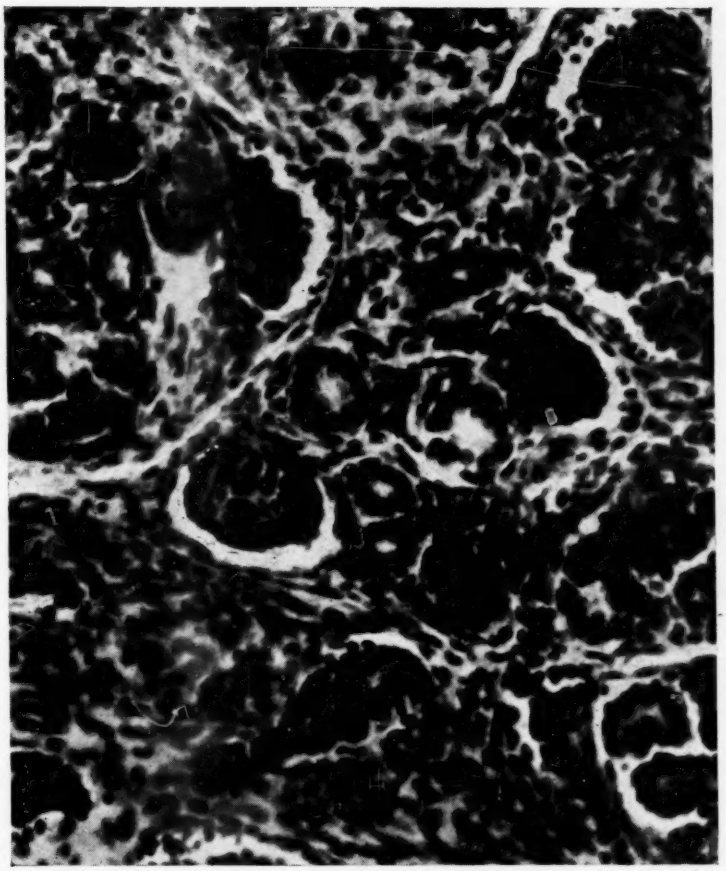

FIG. 2.—Photomicrograph showing embryoma tubules and proglomeruli. ×320.

I wish to thank Professor C. W. Vining for permission to publish this case and for his helpful suggestions.

REFERENCES

Silver, Henry K. (1947). *J. Pediat.*, **31**, 643.
Willis, R. A. (1948). *Pathology of Tumours*, p. 925.

REVIEWS

Observations on the Pathology of Hydrocephalus. By DOROTHY S. RUSSELL, Professor of Pathology in the University of London, and Director of the Bernhard Baron Institute of Pathology, the London Hospital. 1949. M.R.C. Special Report Series No. 265. London: H.M.S.O. Pp. 138. (Price 6*s*.)

In this admirable monograph, Professor Russell has presented an authoritative account of the many and various causes and effects of hydrocephalus. Although much of this information already existed, it has not hitherto been readily available and in collecting and presenting it in this complete and lucid way, Professor Russell has rendered a signal service to knowledge of the subject. The monograph is the outcome of the work of many years, during which the author has had exceptional opportunity for the detailed study of the morbid anatomy of a large number of cases of hydrocephalus. From these cases a selection has been made to provide a comprehensive survey of the pathology of the condition. Clinical particulars are briefly presented. Neoplasms were the commonest cause of hydrocephalus in this series, but meningeal inflammation, whether of bacterial origin or due to haemorrhage or other causes, is recognized as probably responsible for most cases that begin in infancy. In an interesting chapter dealing with maldevelopments, the Arnold-Chiari malformation associated with spina bifida is fully discussed, and the widely held theory of traction is discarded.

The ninety figures nearly all illustrate actual cases. The great majority are photographs, and have been so well chosen and reproduced that they show the conditions illustrated with almost diagrammatic clearness, and are a most valuable feature.

Diagnostic Tests for Infants and Children. By H. BEHRENDT, M.D. 1949. New York and London. Interscience Publishers. Pp. 529. (Price 45*s*.)

This handbook, which deals with the 'principles, clinical and laboratory procedures, and interpretation' of diagnostic tests used in paediatric practice, is the most inclusive of its kind, and is exceptionally well documented. There are special sections on electro-encephalography and intelligence-testing, though the latter, contributed by a different author, is perhaps hardly up to the standard of the rest of the volume. The general method adopted by Dr. Behrendt throughout is to outline the principles of each diagnostic test described, and to discuss the paediatric applications with details of procedure. This book should prove invaluable as a work of reference, and in view of the vast number of additions which have been made to the diagnostic armamentarium of recent years, the author is to be congratulated on successfully covering such a wide field.

Blood Transfusion. Edited by GEOFFREY KEYNES, M.A., M.D., F.R.C.S., Emeritus Surgeon, St. Bartholomew's Hospital. 1949. Bristol: John Wright and Sons. Pp. 586. (Price 52*s*. 6*d*.)

There can be few concerned with any branch of medicine who will not find something to interest them in this comprehensive symposium. The editor has provided an historical survey of the subject, which is a scholarly monograph containing a wealth of picturesque detail, ranging from the aged Pope Innocent VIII drinking the blood of young boys who were sacrificed for the purpose, to the various attempts to use animal donors, and finally to the introduction of citrated blood leading to the modern transfusion era. The indications for transfusion and its complications are dealt with by R. Bodley Scott, who provides nearly a thousand references; the blood groups, the blood donor, and the organization of a hospital transfusion department, by H. F. Brewer, who strays into such pleasant byways as the determination of paternity and the identification of blood stains; and the London Blood Transfusion Service and the psychology of blood donors by F. W. Mills. The technique of blood transfusion is described by Anthony Till, and blood transfusion in infancy by R. W. B. Ellis. Sir Lionel Whitby contributes a chapter on the storage and preservation of blood and blood derivatives, and R. I. N. Greaves one on blood derivatives and blood substitutes. It is not surprising that a book of this magnitude has taken some considerable time to prepare, and that in spite of numerous additions to the proof, some recent work on various aspects of the subject has appeared since the final revision at the end of 1948. Nevertheless, this book assembles a great deal of information which is not readily available elsewhere, and should prove of real value to all those interested in blood transfusion.

A Miniature Textbook of Feeblemindedness. By LEO KANNER, M.D., Director, Children's Psychiatric Service, the Johns Hopkins Hospital. 1949. Child Care Monographs No. 1, Child Care Publications. New York. Pp. 33. (Price $1.25.)

The author, with wit and erudition, examines our concepts of mental deficiency. He concludes that we have as yet no satisfactory classification, and suggests for practical and humanitarian reasons a simple grouping into absolute, relative, and apparent feebleness. His arguments and illustrations are convincing. Six shillings seems a steep price for a paper-covered book of 33 pages (and no index) but it is worth every penny.

Correction: Professor Yoffey writes:—'I note with horror that on page 123 of the June issue I have allowed a very serious error to appear in my paper, since the word "centripetal" should be "centrifugal."'

INDEX TO VOLUME XXIV

PRINTED IN GREAT BRITAIN BY HEADLEY BROTHERS, 109 KINGSWAY, LONDON, W.C.2; AND ASHFORD, KENT